

=> d his

(FILE 'HOME' ENTERED AT 16:34:47 ON 20 JUN 2002)

FILE 'REGISTRY' ENTERED AT 16:35:04 ON 20 JUN 2002

E HEPARIN/CN
 L1 1 S E3 *heparin*
 L2 1 S 81523-64-0
 L3 1 S 50732-58-6 } *claim 16*
 L4 1 S 81523-64-0 } *benzyl ester of heparin*
 L5 1 S 81209-41-8
 E HEPARIN/CN
 L6 1 S SODIUM IMIDAZOLATE/CN
 L7 1 S 5807-14-7
 L8 1 S 81675-81-2 } *cl 17*
 L9 1 S 81675-81-2 } *strong bases*
 L10 1 S 98015-45-3
 L11 67098 S N=3 AND (C AND H AND N)/ELS AND 3/ELC.SUB
 L12 2997 S L11 NOT RSD/FA
 L13 303 S L12 AND "GUANIDINE"
 L14 5504 S L11 AND NR=2 AND NRS=1
 L15 57 S "PYRIMIDO" AND L14
 L16 23 S L15 AND "PYRIMIDINE"
 L17 326 S L13 OR L16
 L18 1 S 5807-14-7
 L19 326 S L17 OR L18
 L20 793 S P=1 AND N=4 AND (C AND H AND N AND P)/ELS AND 4/ELC.SUB
 L21 114 S L20 NOT RSD/FA
 L22 112 S L20 AND NR=1
 L23 1 S SODIUM ACETATE/CN
 L24 1 S HYDROGEN PEROXIDE/CN

search for cl 18

L20-22 search for cl 20

FILE 'HCAPLUS' ENTERED AT 17:06:26 ON 20 JUN 2002

L25 18203 S L1
 L26 13 S L2-5 } *heparin*
 L27 162 S L6
 L28 4638 S L7-10 OR L17 OR L21-22 } *bases*
 L29 18213 S L25-26
 L30 433 S L29(L)RCT/RL *heparin as a RCT*
 L31 4798 S L27-28
 L32 1497 S L31(L)RCT/RL *bases as a RCT*
 L33 1 S L30 AND L32
 L34 1 S 2002:90113/AN *applicant's RCT*
 L35 0 S L33 NOT L34
 L36 43501 S ?HEPARIN?
 L37 255 S L36(S)QUAT?
 L38 860 S L36 (5A)?ESTER?
 L39 20 S L37 AND L38
 L40 9113 S STRONG(3A)(BASE OR BASIC)
 L41 64635 S ?GUANIDIN? OR ?PHOSPHAZEN? OR TRIAZA?
 L42 27070 S PKA
 L43 1 S L39 AND L40-42
 L44 0 S L43 NOT L34
 L45 13 S L37-38 AND L40-42
 L46 16508 S DEPOLYMERI?
 L47 78527 S DE(W)ESTERIF? OR SAPONIF?
 L48 1 S L45 AND L46-47
 L49 0 S L48 NOT L34
 L50 6 S L30 AND L40-42
 L51 1 S L50 AND L46-47

L25-35 searching is based on Registry #'s

L36-L113 searching is mostly based on Free text searching

L25-L86 search is directed to the method of making

L52 156 S L25-26 AND L40-42
 L53 280 S L25-26 AND L46-47
 L54 2 S L52 AND L53
 L55 7 S L50 OR L54
 L56 6 S L55 NOT L34 *6 cites*
 L57 379 S L36 AND L46
 L58 43 S L36 AND L47
 L59 1 S L57 AND L58
 L60 366 S L36(L) L46
 L61 230 S L36(5A) L46
 L62 62 S L61 AND (DE(W)ESTER? OR REMOV? OR CLEAV? OR SAPONIF? OR BASE
 L63 60 S L62 NOT L55
 L64 1 S L63 AND ACETATE
 L65 786430 S SODIUM OR (ALKALAI OR ALKALINE) (2A) (METAL)
 L66 7 S L65 AND L63
 L67 43921 S L25-26 OR L36
 L68 1024 S L67(5A)L65
 L69 117 S L68 AND (DE(W)ESTER? OR REMOV? OR CLEAV? OR SAPONIF? OR BASE
 L70 4 S L69 AND DEPOLYMER?
 L71 2 S L70 NOT L55
 L72 7 S L66 OR L71
 L73 7 S L72 NOT L55 *7 cites*
 E DEPOLYMER/CT
 E E10 +ALL/CT *using some controlled terminology*
 L74 34532 S E3-8
 L75 122 S L74(L) (L47 OR BASE OR BASIC OR PKA OR L28)
 L76 0 S L75 AND (?HEPARIN? OR L25-26)
 L77 54 S L74 AND (?HEPARIN? OR L25-26)
 L78 5 S L77 AND (L47 OR BASE OR BASIC OR PKA OR L28 OR HYDROXIDE)
 L79 4 S L78 NOT (L73 OR L55) *4 cites*
 L80 22 S L68 AND (HYDROLYSIS OR HYDROLI?)
 L81 1 S L80 AND L74
 L82 0 S L81 NOT (L55 OR L73 OR L79)
 L83 31 S L68 AND (HYDROL?)
 L84 30 S L83 NOT (L55 OR L73 OR L79)
 L85 3 S L30 AND L84
 L86 3 S L85 NOT (L55 OR L73 OR L79) *3 cites*
 L87 1263 S (L29 OR ?HEPARIN?) (S)L65
 L88 609523 S KDA OR MW OR MOLECULAR WEIGHT OR KILODALTON OR KDA *L87-L113*
 L89 221 S L88 AND L87 *is directed*
 L90 497 S ANTI-XA *to searching*
 L91 123 S ANTI-IIA *for the*
 L92 311 S ?GLUCURONIC?(S) (END OR TERMIN?) *composition*
 L93 30 S L89 AND L90
 L94 7 S L89 AND L91
 L95 1 S L89 AND L92
 L96 7 S L93 AND L94
 L97 51 S L89 AND XA
 L98 17 S L89 AND IIA
 L99 16 S L97 AND L98
 L100 16 S L96 OR L99
 L101 3 S L100 AND ?URON?
 L102 2 S L101 NOT L34
 L103 13 S L100 NOT L101 *13 cites*
 L104 694 S LMWH
 L105 40 S L104(5A) L87
 L106 35 S L105 NOT (L101 OR L55 OR L73 OR L79 OR L96)
 L107 3 S L106 AND (?URON? OR ?SULPHAT? OR ?SULFAT?) *3 cites*
 L108 1 S L87 AND L92
 L109 25 S (L29 OR ?HEPARIN?) AND L92

KRISHNAN 09/909,797

| | |
|------|--------------------------------------|
| L110 | 14 S L109 AND (L88 OR L104 OR VLMWH) |
| L111 | 2 S L110 AND (XA OR IA OR L90-91) |
| L112 | 1 S L111 NOT L34 <i>1 cite</i> |
| L113 | 12 S L110 NOT L111 <i>12 cites</i> |

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(FILE 'HOME' ENTERED AT 14:20:46 ON 20 JUN 2002)

FILE 'HCAPLUS' ENTERED AT 14:20:54 ON 20 JUN 2002

L1 3 S PECQUET C?/AU
L2 78 S PERRIN E?/AU
L3 844 S DIAZ J?/AU
L4 7 S VISKOV C?/AU
L5 927 S L1-4
L6 5 S L5 AND HEPARIN
L7 1 S L6 AND METAL
SELECT L7 1 RN

FILE 'REGISTRY' ENTERED AT 14:23:38 ON 20 JUN 2002

L8 9 S E1-9

FILE 'HCAPLUS' ENTERED AT 14:23:44 ON 20 JUN 2002

L9 1 S L7 AND L8
L10 4 S L6 NOT L9
SELECT RN L10 1-4

1 cite w/ 9 cpds displayed

FILE 'REGISTRY' ENTERED AT 14:27:02 ON 20 JUN 2002

L11 42 S E10-51

FILE 'HCAPLUS' ENTERED AT 14:27:28 ON 20 JUN 2002

L12 4 S L10 AND L11

4 cites

KRISHNAN 09/909,797

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L9 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:90113 HCAPLUS

DOCUMENT NUMBER: 136:153008

TITLE: **Heparin**-derived polysaccharide mixtures,
preparation method and pharmaceutical compositions
containing same

INVENTOR(S): **Diaz, Jacques; Pecquet, Christelle**
; **Perrin, Elisabeth; Viskov,**
Christian

PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|------------|
| WO 2002008295 | A1 | 20020131 | WO 2001-FR2332 | 20010718 |
| <p>W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM</p> <p>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG</p> | | | | |
| FR 2811992 | A1 | 20020125 | FR 2000-9572 | 20000721 |
| US 2002055621 | A1 | 20020509 | US 2001-909797 | 20010723 |
| PRIORITY APPLN. INFO.: | | | FR 2000-9572 | A 20000721 |
| | | | US 2000-229123P | P 20000831 |

OTHER SOURCE(S): MARPAT 136:153008

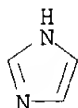
AB The invention concerns **heparin**-derived polysaccharide mixts. having mol. wt. 1500-3000, anti-Xa activity 100-150 UI/mg, anti IIa activity 0-10 UI/mg, anti-Xa activity/anti-IIa activity >10, 2-26 saccharide groups, 4,5-glucuronic 2-O-sulfate terminal groups, under alkali or alk.-earth **metal** salt form. These mixts. are manufd. by depolymn. of quaternary ammonium salts of benzyl esters of **heparin** in org. solvent using a strong org. base having pKa >20 or Na imidazolate, transforming the resulting quaternary ammonium salt of the depolymd. benzylic ester to the Na salt, and sapon. of the ester.

IT **5587-42-8**, Sodium imidazolate **5807-14-7**,
1,5,7-Triazabicyclo[4.4.0]dec-5-ene **81675-81-2**
98015-45-3

RL: RCT (Reactant); RACT (Reactant or reagent)
(depolymer. agent; **heparin**-derived polysaccharide mixts. with
improved anticoagulant and antithrombic activity)

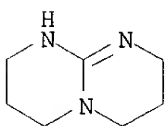
RN 5587-42-8 HCAPLUS

CN 1H-Imidazole, sodium salt (9CI) (CA INDEX NAME)

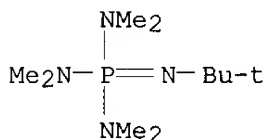


Na

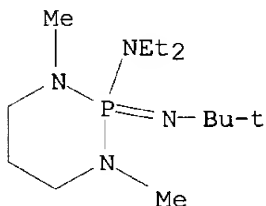
RN 5807-14-7 HCAPLUS
CN 2H-Pyrimido[1,2-a]pyrimidine, 1,3,4,6,7,8-hexahydro- (6CI, 8CI, 9CI) (CA INDEX NAME)



RN 81675-81-2 HCAPLUS
CN Phosphorimidic triamide, N'''-(1,1-dimethylethyl)-N,N,N',N',N'',N''-hexamethyl- (9CI) (CA INDEX NAME)



RN 98015-45-3 HCAPLUS
CN 1,3,2-Diazaphosphorin-2(1H)-amine, 2-[(1,1-dimethylethyl)imino]-N,N-diethyl-2,2,3,4,5,6-hexahydro-1,3-dimethyl- (9CI) (CA INDEX NAME)



IT 81523-64-0DP, depolymd., saponid.
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); BIOL (Biological study); PREP (Preparation)
(heparin-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)
RN 81523-64-0 HCAPLUS
CN Heparin, phenylmethyl ester, ion (neg.), N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]benzenemethanaminium (9CI) (CA INDEX NAME)

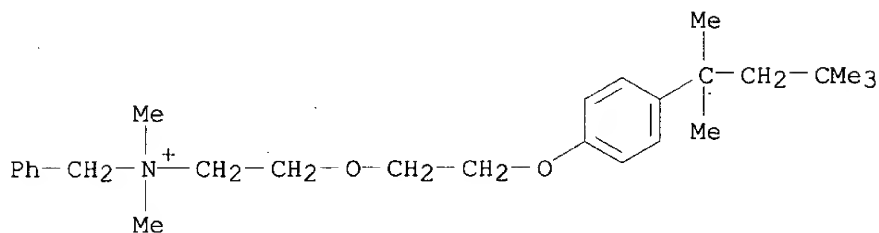
CM 1

CRN 81405-95-0
 CMF Unspecified
 CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 10172-60-8
 CMF C27 H42 N O2



IT 50732-58-6P, preparation 81523-64-0P

RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT
 (Reactant or reagent)

(precursor; **heparin**-derived polysaccharide mixts. with
 improved anticoagulant and antithrombic activity)

RN 50732-58-6 HCAPLUS

CN Heparin, ion (neg.), N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-
 tetramethylbutyl)phenoxy]ethoxy]ethyl]benzenemethanaminium (9CI) (CA
 INDEX NAME)

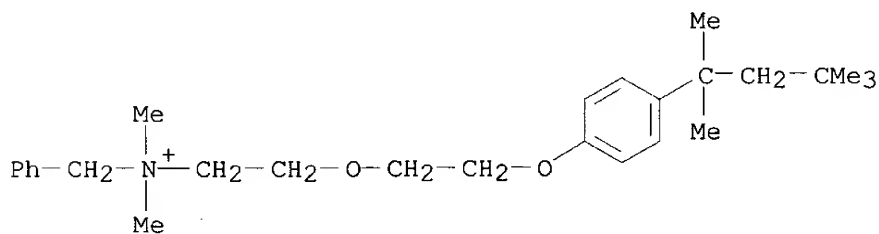
CM 1

CRN 51053-42-0
 CMF Unspecified
 CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 10172-60-8
 CMF C27 H42 N O2



RN 81523-64-0 HCAPLUS

CN Heparin, phenylmethyl ester, ion (neg.), N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-

tetramethylbutyl)phenoxy]ethoxy]ethyl]benzenemethanaminium (9CI) (CA INDEX NAME)

CM 1

CRN 81405-95-0

CMF Unspecified

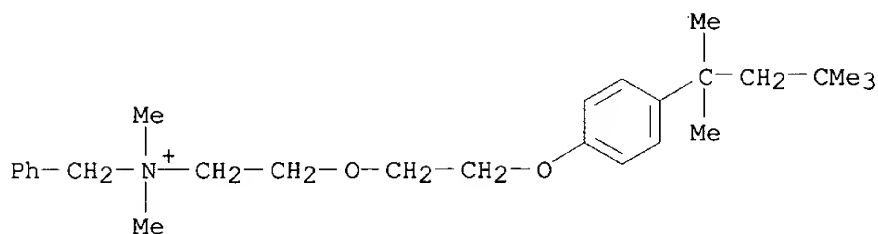
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 10172-60-8

CMF C27 H42 N O2



IT 100-44-7, Benzyl chloride, reactions 121-54-0,

Benzethonium chloride 81209-41-8

RL: RCT (Reactant); RACT (Reactant or reagent)

(precursor; **heparin**-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)

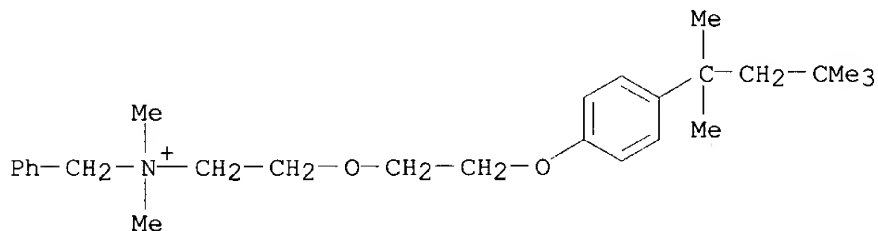
RN 100-44-7 HCAPLUS

CN Benzene, (chloromethyl)- (9CI) (CA INDEX NAME)

Ph-CH₂-Cl

RN 121-54-0 HCAPLUS

CN Benzenemethanaminium, N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]-, chloride (9CI) (CA INDEX NAME)



Cl⁻

RN 81209-41-8 HCAPLUS

CN Heparin, phenylmethyl ester, sodium salt (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-51-6
CMF C7 H8 O

HO-CH₂-Ph

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L9 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS
IC ICM C08B037-10
ICS A61K031-727
CC 44-5 (Industrial Carbohydrates)
Section cross-reference(s): 1, 63
ST benzyl ester **heparin** quaternary ammonium salt depolymn strong base; anticoagulant activity enhanced depolymd **heparin**; antithrombic activity enhanced depolymd **heparin**
IT Phosphazenes
RL: RCT (Reactant); RACT (Reactant or reagent)
(depolymn. agent; **heparin**-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)
IT Anticoagulants
(**heparin**-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)
IT Polysaccharides, preparation
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); BIOL (Biological study); PREP (Preparation)
(**heparin**-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)
IT 5587-42-8, Sodium imidazolate 5807-14-7, 1,5,7-Triazabicyclo[4.4.0]dec-5-ene 81675-81-2 98015-45-3
RL: RCT (Reactant); RACT (Reactant or reagent).
(depolymn. agent; **heparin**-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)
IT 81523-64-0DP, depolymd., saponid.
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); BIOL (Biological study); PREP (Preparation)
(**heparin**-derived polysaccharide mixts. with improved anticoagulant and antithrombic activity)
IT 50732-58-6P, preparation 81523-64-0P
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(precursor; **heparin**-derived polysaccharide mixts. with

improved anticoagulant and antithrombic activity)
IT 100-44-7, Benzyl chloride, reactions 121-54-0,
Benzethonium chloride 81209-41-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(precursor; **heparin**-derived polysaccharide mixts. with
improved anticoagulant and antithrombic activity)

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L10 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:730755 HCAPLUS

DOCUMENT NUMBER: 135:273169

TITLE: Preparation of uronic acid-containing oligosaccharides
as antiinflammatory agentsINVENTOR(S): Mourier, Pierre; Perrin, Elisabeth;
Viskov, Christian

PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.

SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2001072762 | A1 | 20011004 | WO 2001-FR903 | 20010326 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

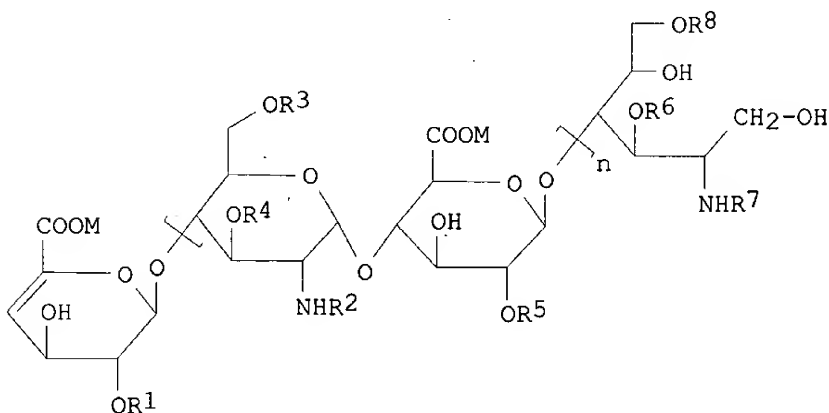
| | | | | |
|------------|----|----------|--------------|----------|
| FR 2807043 | A1 | 20011005 | FR 2000-3910 | 20000328 |
|------------|----|----------|--------------|----------|

| | | | | |
|---------------|----|----------|----------------|----------|
| US 2002019368 | A1 | 20020214 | US 2001-817428 | 20010326 |
|---------------|----|----------|----------------|----------|

| | | | |
|------------------------|--------------|---|----------|
| PRIORITY APPLN. INFO.: | FR 2000-3910 | A | 20000328 |
|------------------------|--------------|---|----------|

OTHER SOURCE(S): MARPAT 135:273169

GI



AB Uronic acid-contg. oligosaccharides I ($n = 0-25$; R1, R3-R6, R8 are independently H, SO₃M; R2, R7 independently H, SO₃M, COMe; M is Na, Ca, Mg, K, oligosaccharide) were prepd. from **heparin** as antiinflammatory agents. Thus, I ($n = 1$; R1-R3 = R5 = R7-R8 = SO₃Na; R4 =

R6 = H) was prepd. and tested in mice as antiinflammatory agent.
 REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L12 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS

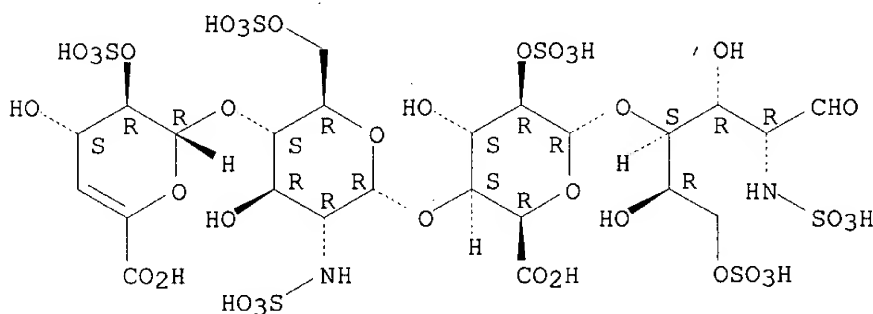
IT 96849-33-1P 333796-83-1P 333796-84-2P
 333796-85-3P 363148-40-7P 363148-42-9P
 363148-43-0P 363148-44-1P 363148-45-2P
 363148-48-5P 363148-49-6P 363148-51-0P
 363148-52-1P 363148-53-2P 363595-83-9P
 363595-85-1P

RL: BAC (Biological activity or effector, except adverse); BPN
 (Biosynthetic preparation); BSU (Biological study, unclassified); IMF
 (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic
 use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of uronic acid-contg. oligosaccharides from **heparin**
 as antiinflammatory agents)

RN 96849-33-1 HCAPLUS

CN D-Glucose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-
 (1.fwdarw.4)-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-
 (1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-
 (sulfoamino)-, 6-(hydrogen sulfate), octasodium salt (9CI) (CA INDEX
 NAME)

Absolute stereochemistry.



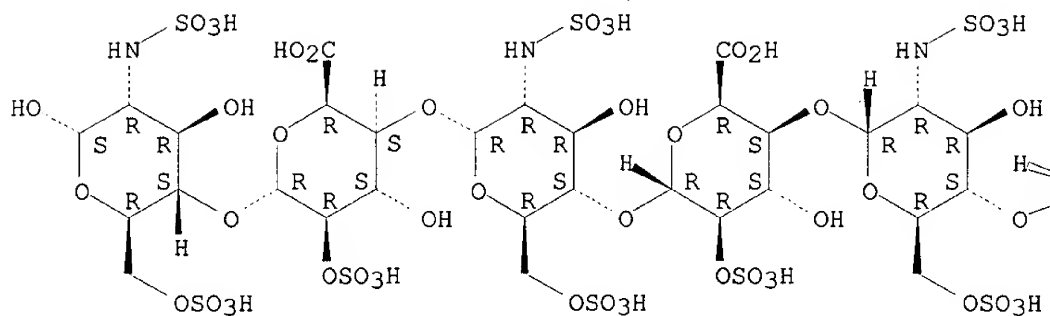
● 8 Na

RN 333796-83-1 HCAPLUS

CN .alpha.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-
 enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-
 glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-
 (1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-
 (1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-
 (sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX
 NAME)

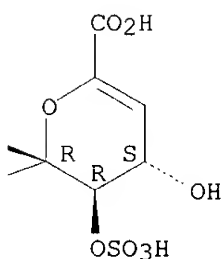
Absolute stereochemistry.

PAGE 1-A



● 12 Na

PAGE 1-B

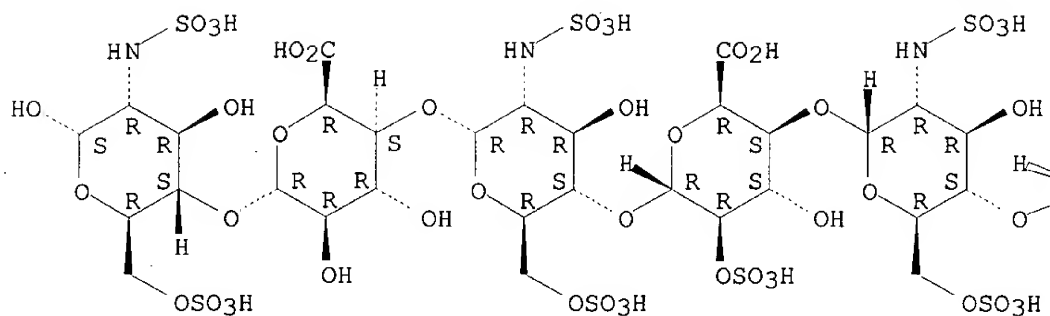


RN 333796-84-2 HCAPLUS

CN .alpha.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), undecasodium salt (9CI) (CA INDEX NAME)

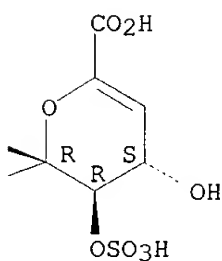
Absolute stereochemistry.

PAGE 1-A



● 11 Na

PAGE 1-B

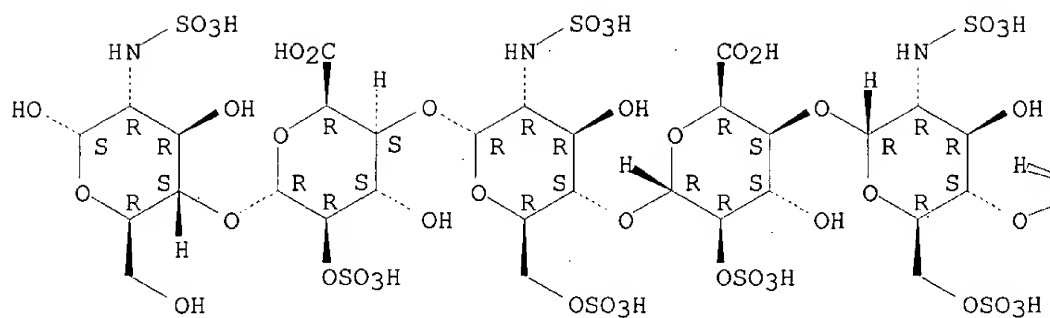


RN 333796-85-3 HCAPLUS

CN .alpha.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, undecasodium salt (9CI) (CA INDEX NAME)

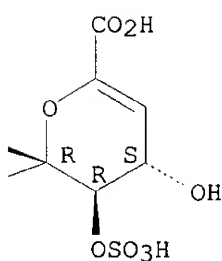
Absolute stereochemistry.

PAGE 1-A



● 11 Na

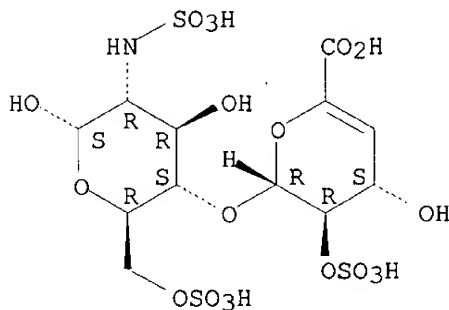
PAGE 1-B



RN 363148-40-7 HCAPLUS

CN .alpha.-D-Glucopyranose, 2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

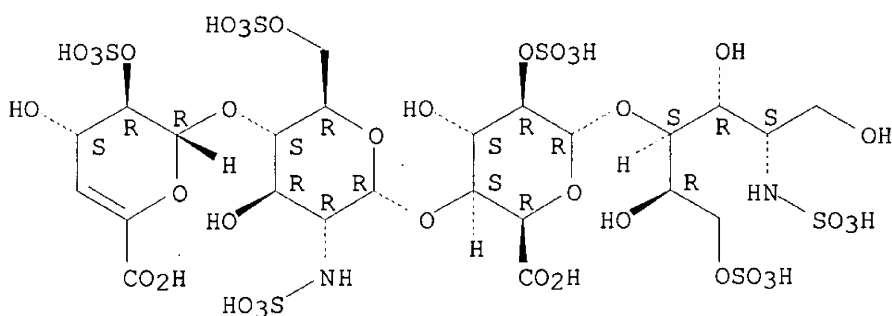


4 Na

RN 363148-42-9 HCAPLUS

CN D-Glucitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), octasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

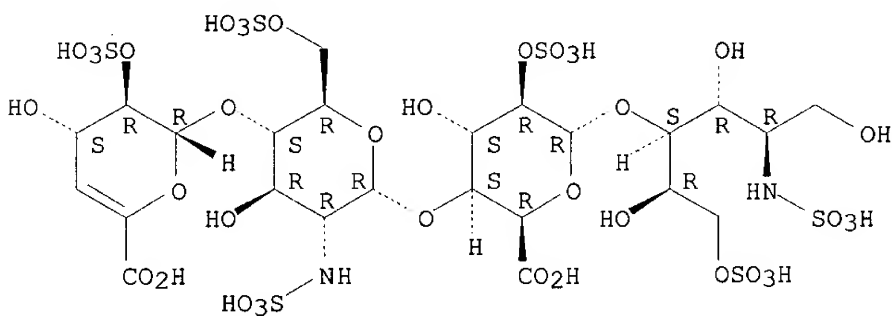


●8 Na

RN 363148-43-0 HCAPLUS

CN D-Mannitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), octasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



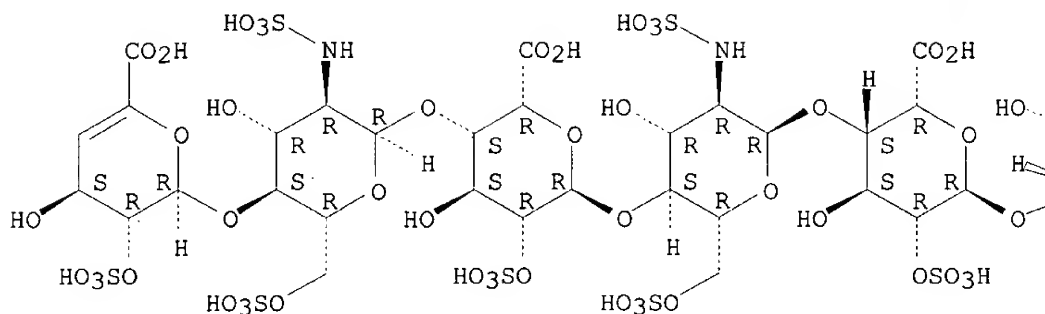
●8 Na

RN 363148-44-1 HCAPLUS

CN D-Glucitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX NAME)

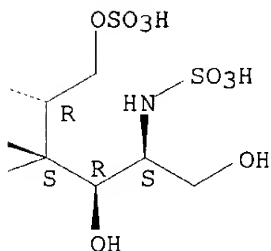
Absolute stereochemistry.

PAGE 1-A



● 12 Na

PAGE 1-B

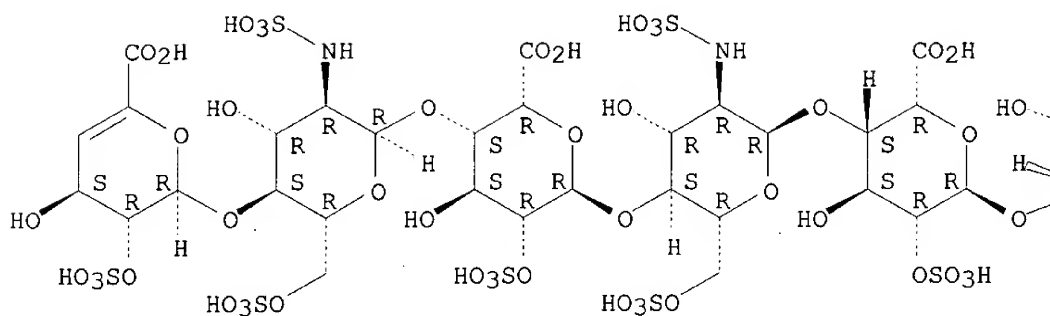


RN 363148-45-2 HCAPLUS

CN D-Mannitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX NAME)

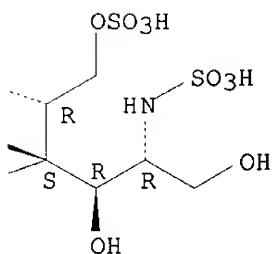
Absolute stereochemistry.

PAGE 1-A



● 12 Na

PAGE 1-B

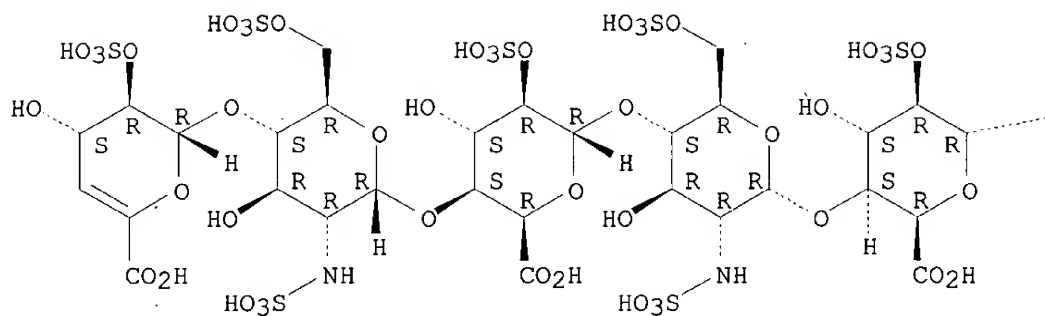


RN 363148-48-5 HCAPLUS

CN D-Glucitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), hexadecasodium salt (9CI) (CA INDEX NAME)

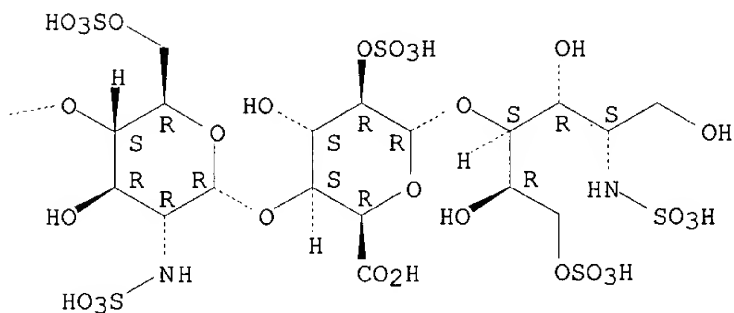
Absolute stereochemistry.

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● 16 Na

PAGE 1-B

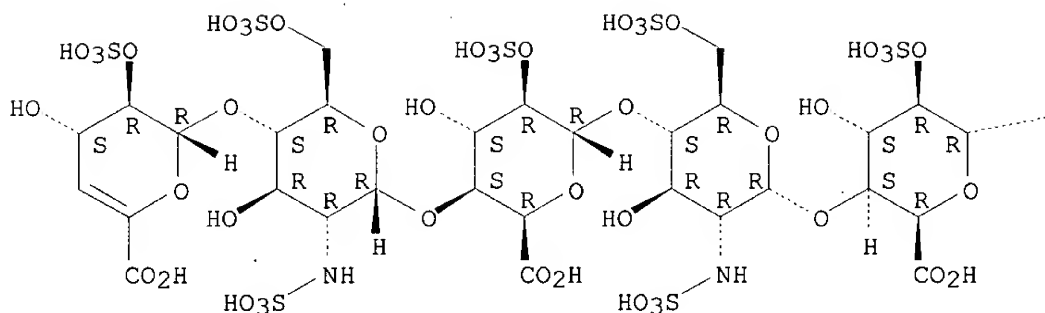


RN 363148-49-6 HCAPLUS

CN D-Mannitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), hexadecasodium salt (9CI) (CA INDEX NAME)

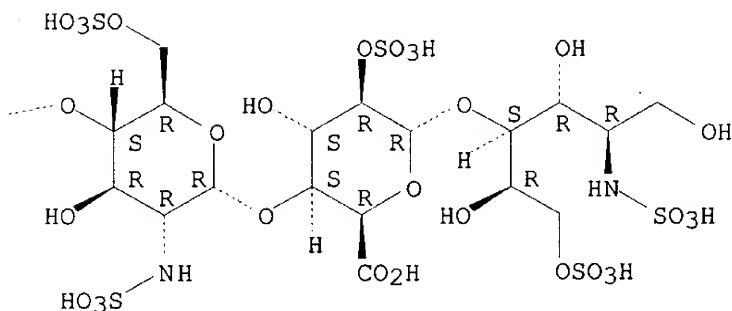
Absolute stereochemistry.

PAGE 1-A



● 16 Na

PAGE 1-B

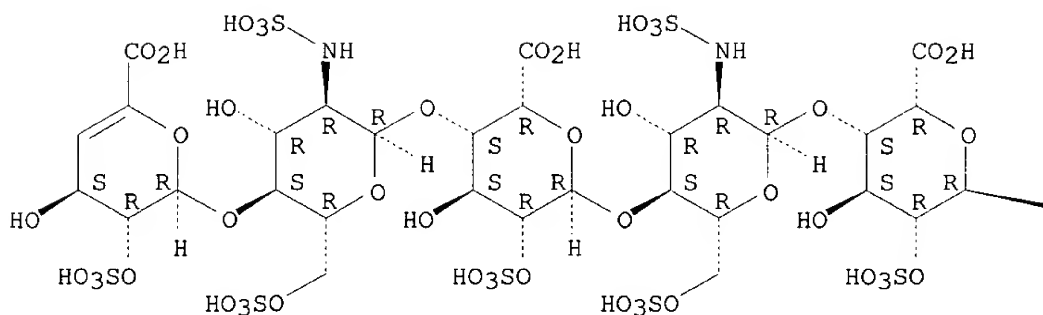


RN 363148-51-0 HCAPLUS

CN D-Mannose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), eicosasodium salt (9CI) (CA INDEX NAME)

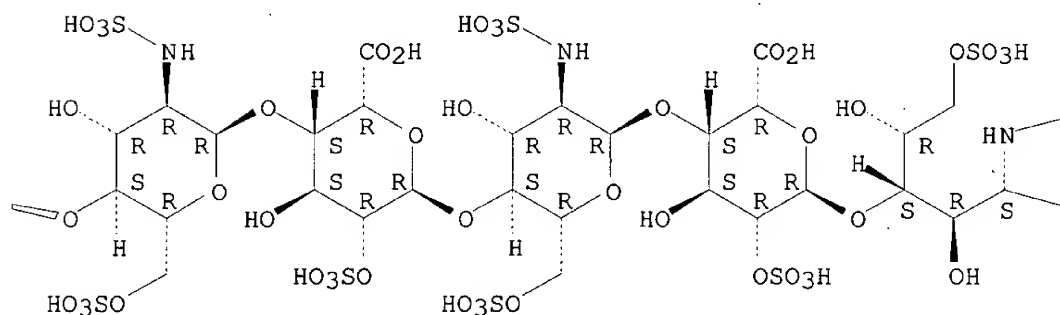
Absolute stereochemistry.

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● 20 Na

PAGE 1-B



PAGE 1-C

—SO₃H

—CHO

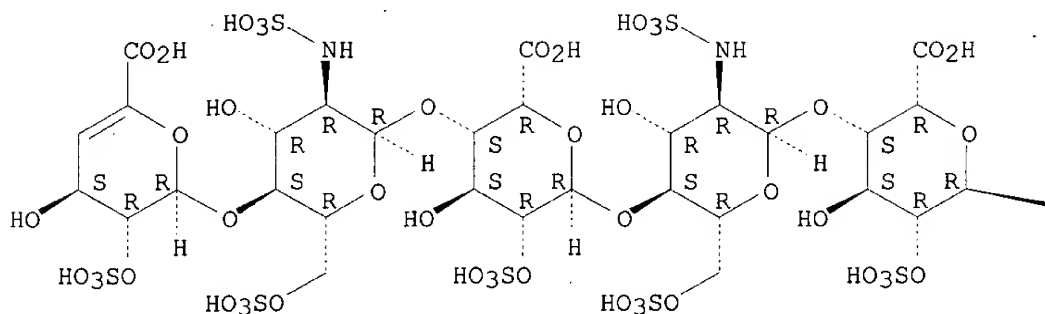
RN 363148-52-1 HCAPLUS

CN D-Glucitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), eicosasodium

salt (9CI) (CA INDEX NAME)

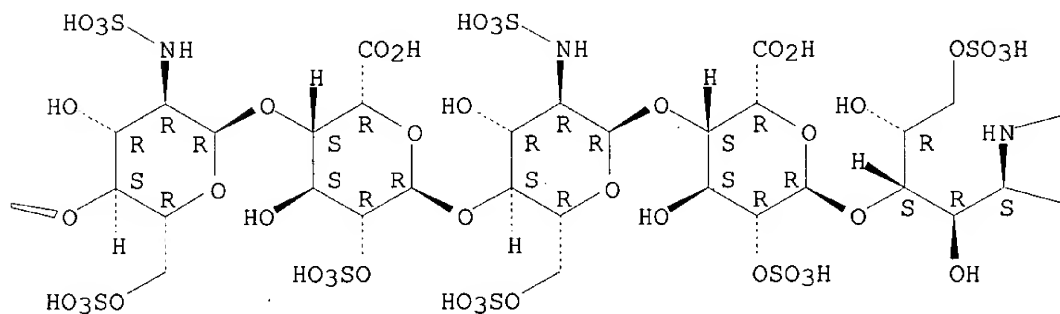
Absolute stereochemistry.

PAGE 1-A



● 20 Na

PAGE 1-B



PAGE 1-C

—SO₃H

—OH

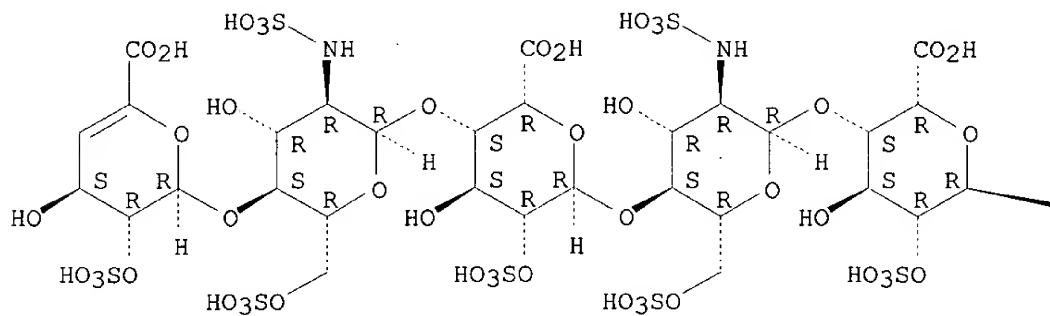
RN 363148-53-2 HCAPLUS

CN D-Mannitol, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-

idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), eicosasodium salt (9CI) (CA INDEX NAME)

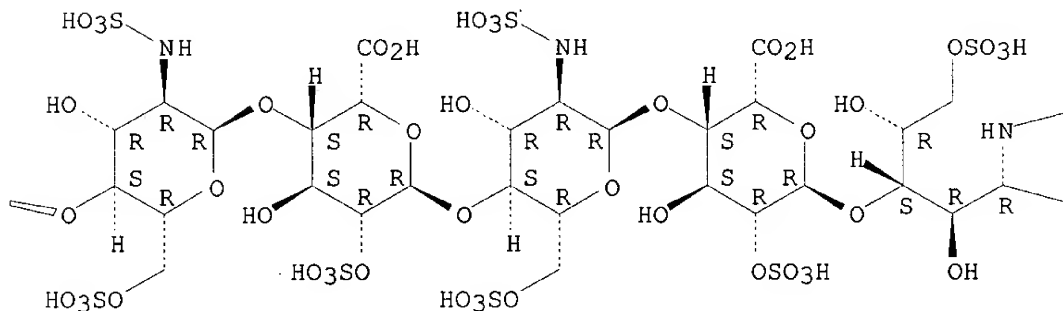
Absolute stereochemistry.

PAGE 1-A



● 20 Na

PAGE 1-B



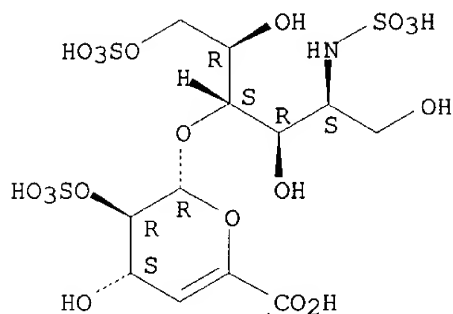
PAGE 1-C

—SO₃H

—OH

RN 363595-83-9 HCAPLUS
CN D-Glucitol, 2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

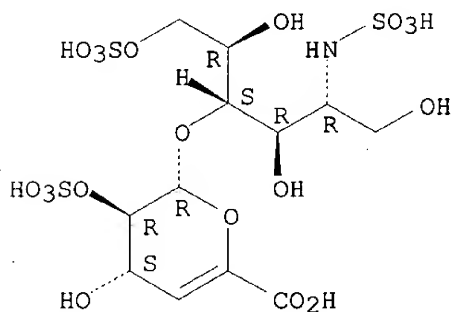


● 4 Na

RN 363595-85-1 HCAPLUS

CN D-Mannitol, 2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 4 Na

IT 9025-39-2, Heparinase I

RL: CAT (Catalyst use); USES (Uses)

(prepn. of uronic acid-contg. oligosaccharides from **heparin** as antiinflammatory agents)

RN 9025-39-2 HCAPLUS

CN Lyase, heparin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9005-49-6, **Heparin**, reactions 136098-10-7

161729-25-5 164082-52-4 164082-54-6

340154-98-5 340156-51-6 363148-41-8

363148-47-4

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of uronic acid-contg. oligosaccharides from **heparin** as antiinflammatory agents)

RN 9005-49-6 HCAPLUS

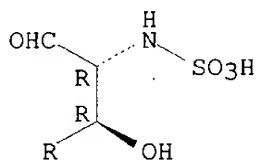
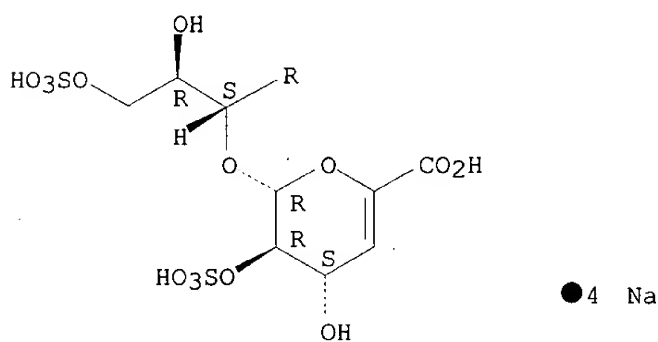
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 136098-10-7 HCAPLUS

CN D-Glucose, 2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

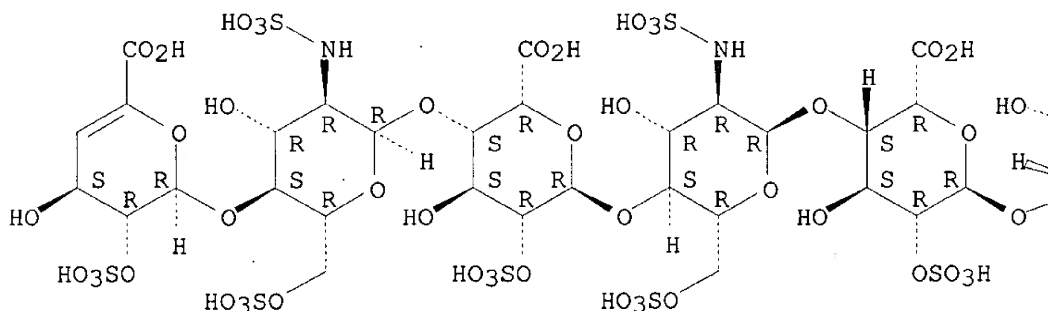


RN 161729-25-5 HCAPLUS

CN D-Glucose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX NAME)

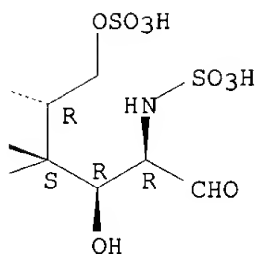
Absolute stereochemistry.

PAGE 1-A



12 Na

PAGE 1-B

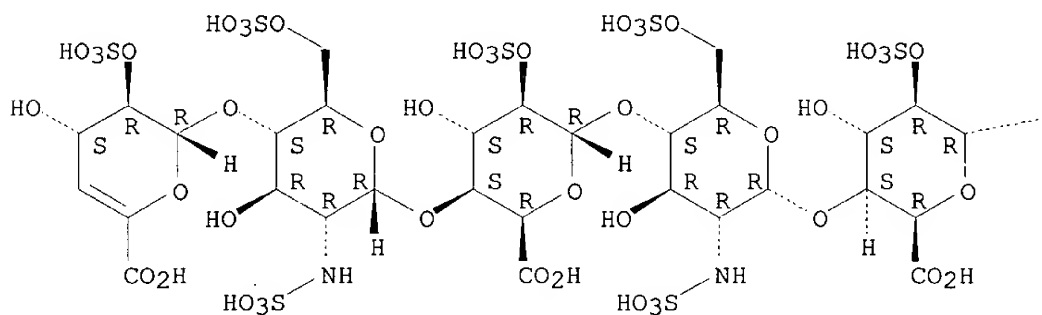


RN 164082-52-4 HCAPLUS

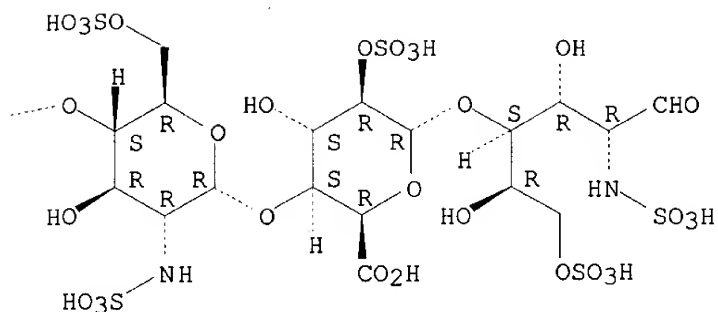
CN D-Glucose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), hexadecasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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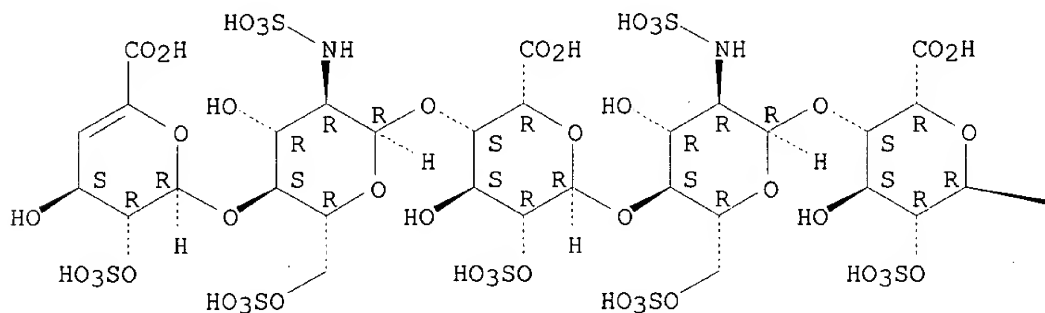
● 16 Na



RN 164082-54-6 HCAPLUS

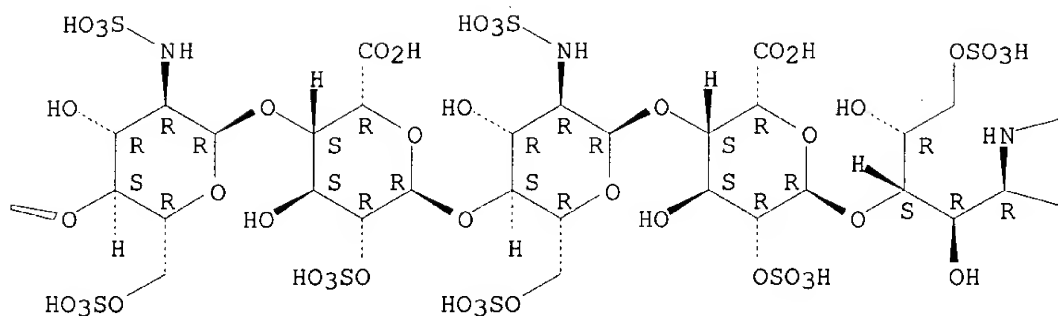
CN D-Glucose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), eicosasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 20 Na

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PAGE 1-C

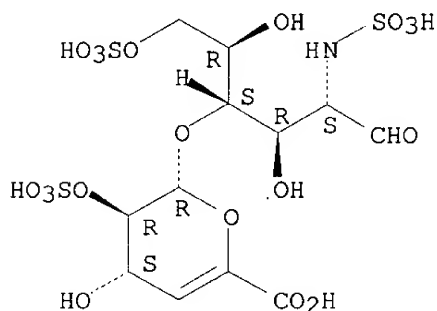
—SO₃H

—CHO

RN 340154-98-5 HCAPLUS

CN D-Mannose, 2-deoxy-4-O-(4-deoxy-2-O-sulfo-α-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



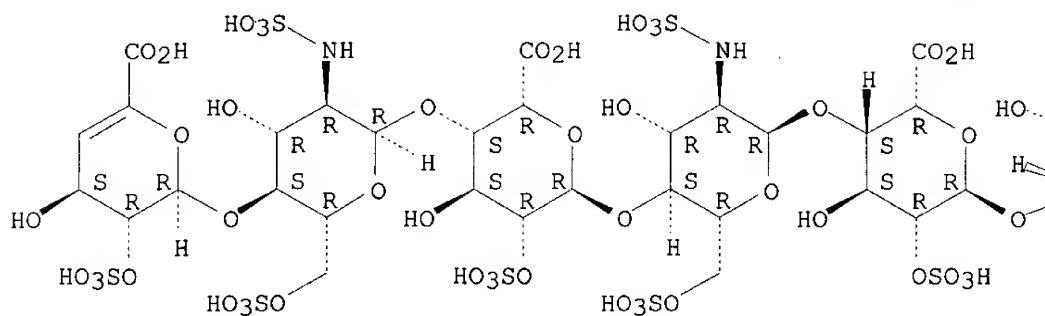
●4 Na

RN 340156-51-6 HCAPLUS

CN D-Mannose, O-4-deoxy-2-O-sulfo-α-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX NAME)

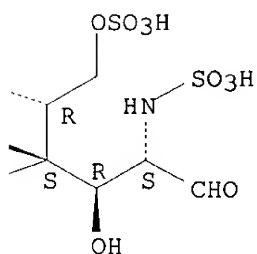
Absolute stereochemistry.

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● 12 Na

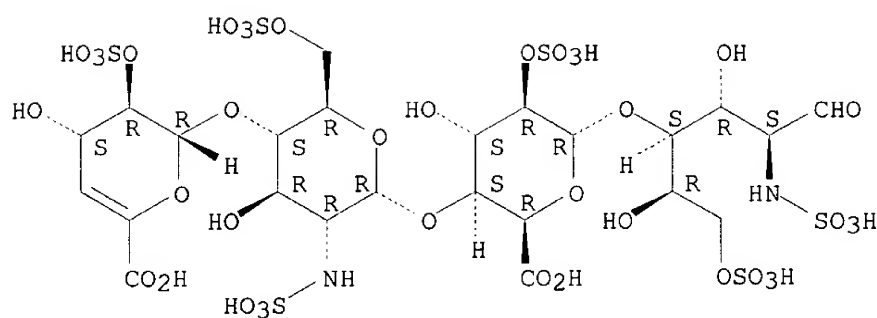
PAGE 1-B



RN 363148-41-8 HCAPLUS

CN D-Mannose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), octasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



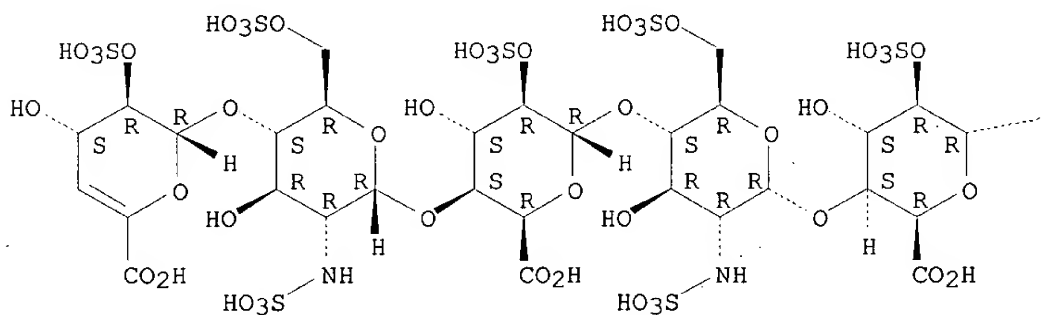
● 8 Na

RN 363148-47-4 HCAPLUS

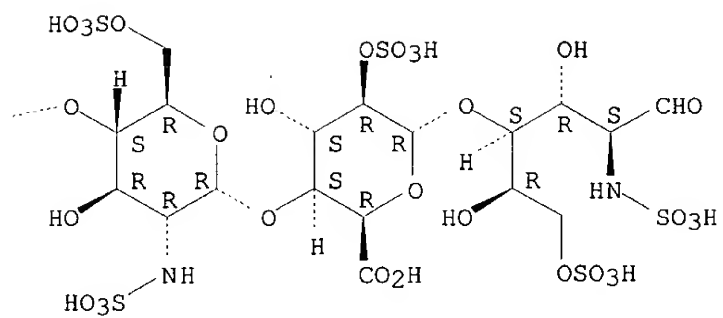
CN D-Mannose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), hexadecasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



● 16 Na



=> d ibib abs hitstr 2

L12 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:300732 HCAPLUS

DOCUMENT NUMBER: 134:281073

TITLE: Preparation of uronic acid-containing oligosaccharides as antiinflammatory agents.

INVENTOR(S): Mourier, Pierre; Perrin, Elisabeth;
Viskov, Christian; Stutzmann, Jean-marie;
Wahl, Florence

PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.

SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

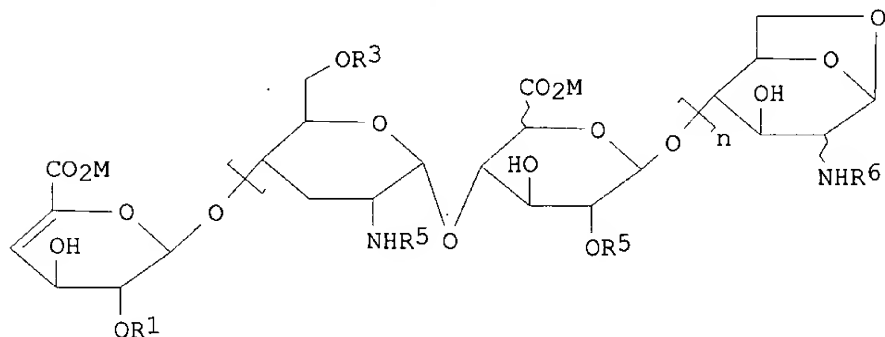
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2001029055 | A2 | 20010426 | WO 2000-FR2897 | 20001018 |
| WO 2001029055 | A3 | 20020214 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| FR 2800074 | A1 | 20010427 | FR 1999-13182 | 19991022 |
| FR 2800074 | B1 | 20011221 | | |

PRIORITY APPLN. INFO.: FR 1999-13182 A 19991022

OTHER SOURCE(S): CASREACT 134:281073; MARPAT 134:281073

GI



I

AB The invention concerns oligosaccharides I wherein n is 0-25; R1, R3-R5 are identical or different and represent H, SO3M; R2, R6 are identical or different and represent H, SO3M, COMe; M is Na, Ca, Mg, K; their diastereomers, methods for prep. them as antiinflammatory agents. Thus,.

4-Deoxy-2-O-sulfoanda-L-threo-hex-4-enopyranosyluronate-(1-4)-2-deoxy-2-sulfoamino-6-O-sulfo-D-glucopyranosyl-(1-4)-2-O-sulfo-aX-L-idopyranosyluronate-(1-4)-2-deoxy-2-sulfoamino-6-O-sulfo-D-glucopyranosyl-(1-4)-O-sulfo-ca-L-idopyranosyluronate-(1-4)-1,6-anhydro-2-deoxy-2-sulfoamino-3-D-glucopyranose undeca-sodium salt was prepd. and tested in rats as antiinflammatory agent.

IT 98797-51-4P 333796-82-0P 333796-83-1P
333796-84-2P 333796-85-3P 333796-86-4P
333796-87-5P 333796-88-6P 333796-89-7P

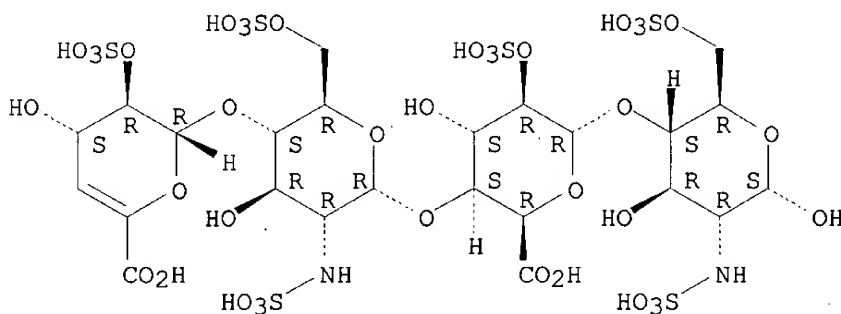
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of uronic acid-contg. oligosaccharides as antiinflammatory agents)

RN 98797-51-4 HCAPLUS

CN .alpha.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), octasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

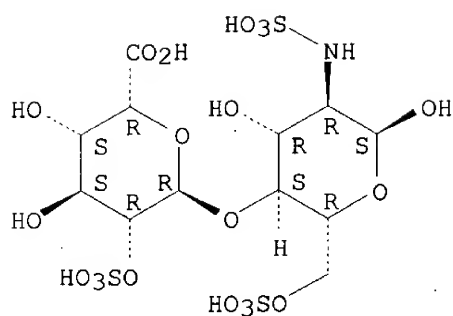


● 8 Na

RN 333796-82-0 HCAPLUS

CN .alpha.-D-Glucopyranose, 2-deoxy-2-(sulfoamino)-4-O-(2-O-sulfo-.alpha.-L-idopyranuronosyl)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

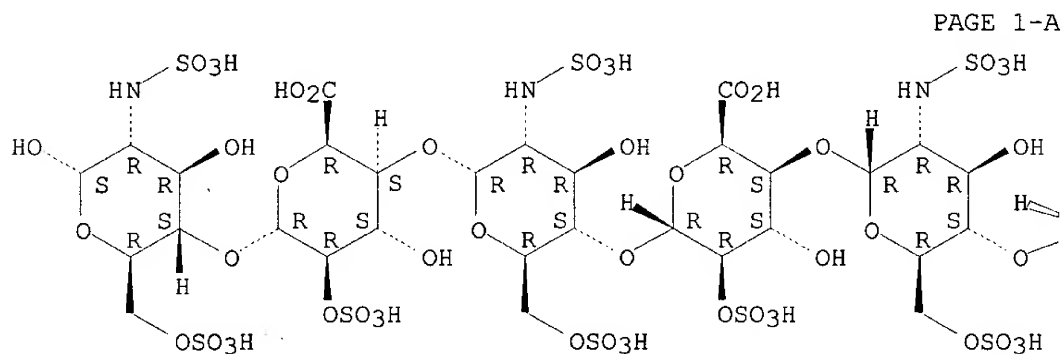


● 4 Na

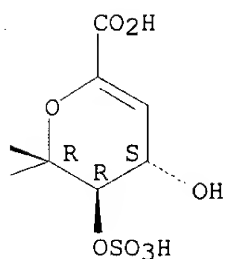
RN 333796-83-1 HCAPLUS

CN .alpha.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 12 Na

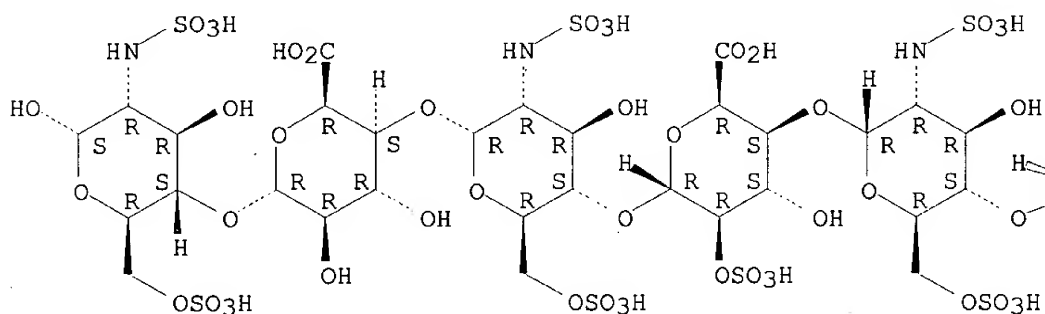


RN 333796-84-2 HCAPLUS

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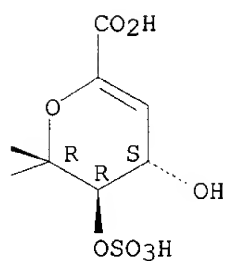
Absolute stereochemistry.

PAGE 1-A



● 11 Na

PAGE 1-B

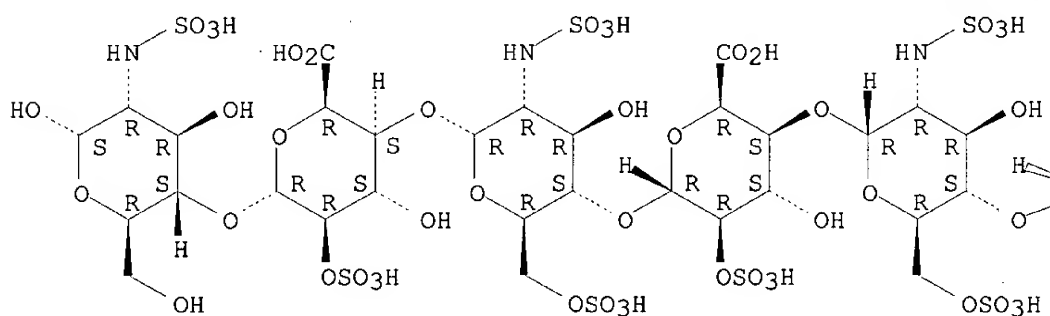


RN 333796-85-3 HCAPLUS

CN .alpha.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, undecasodium salt (9CI) (CA INDEX NAME)

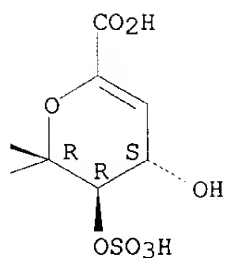
Absolute stereochemistry.

PAGE 1-A



● 11 Na

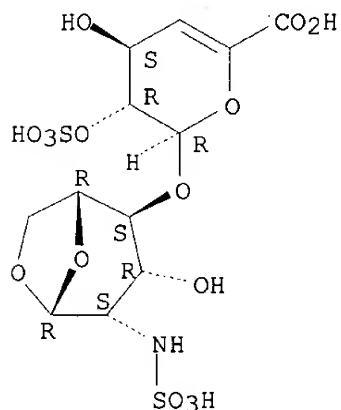
PAGE 1-B



RN 333796-86-4 HCAPLUS

CN .beta.-D-Mannopyranose, 1,6-anhydro-2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, trisodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

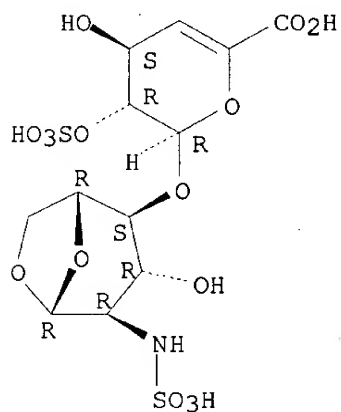


●3 Na

RN 333796-87-5 HCAPLUS

CN .beta.-D-Glucopyranose, 1,6-anhydro-2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, trisodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



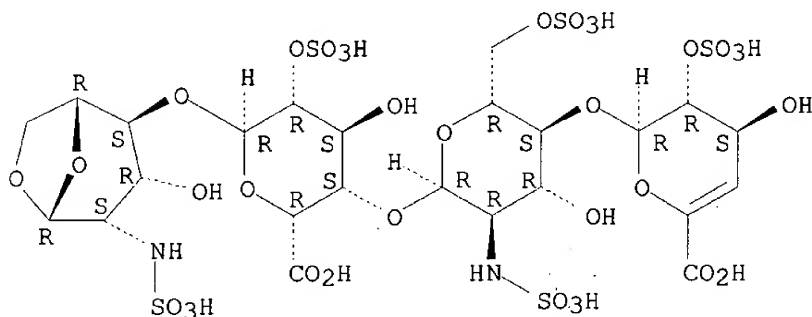
●3 Na

RN 333796-88-6 HCAPLUS

CN .beta.-D-Mannopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-

glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-
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(CA INDEX NAME)

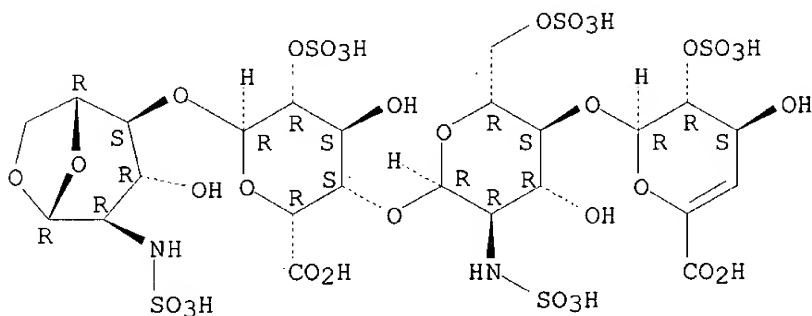
Absolute stereochemistry.



●7 Na

RN 333796-89-7 HCAPLUS
CN .beta.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-
enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-
glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-
(1.fwdarw.4)-1,6-anhydro-2-deoxy-2-(sulfoamino)-, heptasodium salt (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

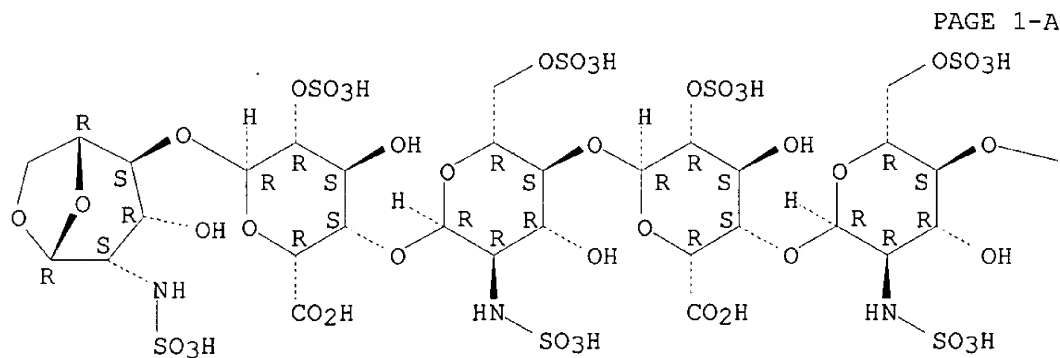


●7 Na

IT 333796-90-0P 333796-91-1P 333796-92-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of uronic acid-contg. oligosaccharides as antiinflammatory
agents)
RN 333796-90-0 HCAPLUS
CN .beta.-D-Mannopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-
enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-

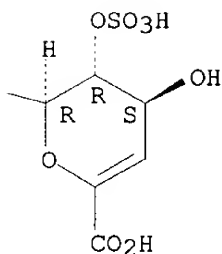
glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-
 (1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-
 (1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-1,6-
 anhydro-2-deoxy-2-(sulfoamino)-, undecasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 11 Na

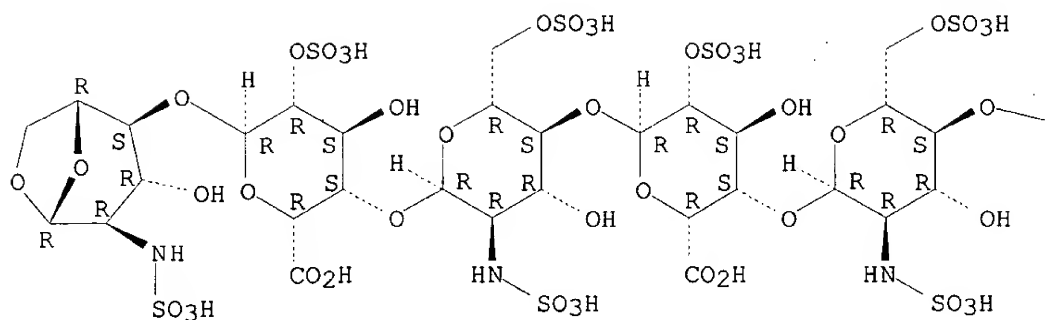
PAGE 1-B



RN 333796-91-1 HCAPLUS
 CN .beta.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-
 enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-
 glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-
 (1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-
 (1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-1,6-
 anhydro-2-deoxy-2-(sulfoamino)-, undecasodium salt (9CI) (CA INDEX NAME)

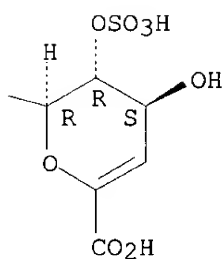
Absolute stereochemistry.

PAGE 1-A



● 11 Na

PAGE 1-B

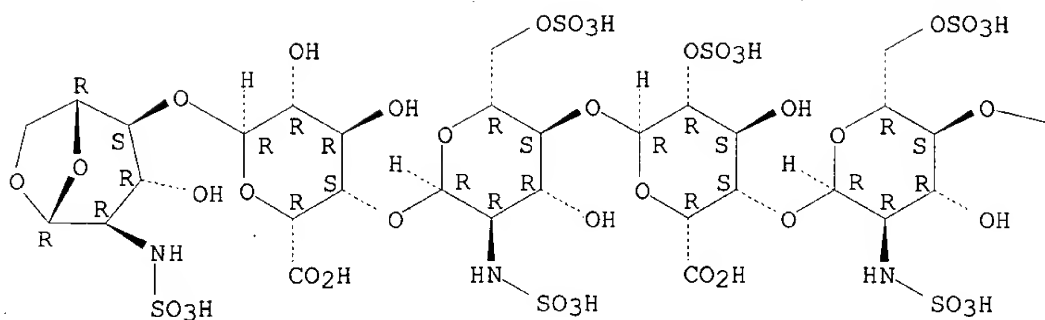


RN 333796-92-2 HCAPLUS

CN .beta.-D-Glucopyranose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-1,6-anhydro-2-deoxy-2-(sulfoamino)-, decasodium salt (9CI) (CA INDEX NAME)

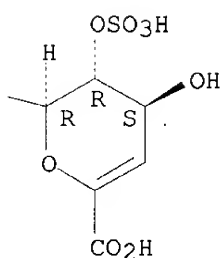
Absolute stereochemistry.

PAGE 1-A



● 10 Na

PAGE 1-B



IT 9025-39-2, Heparinase I
 RL: CAT (Catalyst use); USES (Uses)
 (prepn. of uronic acid-contg. oligosaccharides as antiinflammatory agents)
 RN 9025-39-2 HCAPLUS
 CN Lyase, heparin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 1310-58-3, Potassium hydroxide, reactions 1310-65-2,
 Lithium hydroxide 1310-73-2, Sodium hydroxide, reactions
 2052-49-5, Tetrabutylammonium hydroxide 9005-49-6,
 Heparin, reactions 21351-79-1, Cesium hydroxide
 340154-98-5 340156-51-6
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (prepn. of uronic acid-contg. oligosaccharides as antiinflammatory agents)
 RN 1310-58-3 HCAPLUS
 CN Potassium hydroxide (K(OH)) (9CI) (CA INDEX NAME)

K-OH

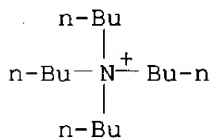
RN 1310-65-2 HCAPLUS
 CN Lithium hydroxide (Li(OH)) (9CI) (CA INDEX NAME)

Li-OH

RN 1310-73-2 HCAPLUS
 CN Sodium hydroxide (Na(OH)) (9CI) (CA INDEX NAME)

Na-OH

RN 2052-49-5 HCAPLUS
 CN 1-Butanaminium, N,N,N-tributyl-, hydroxide (9CI) (CA INDEX NAME)



● OH⁻

RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

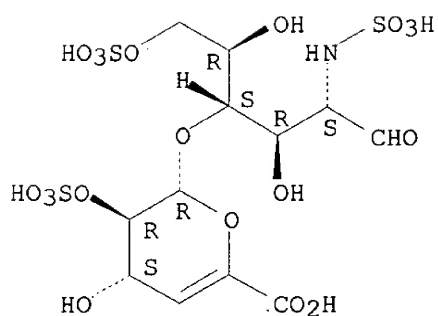
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 21351-79-1 HCAPLUS
 CN Cesium hydroxide (Cs(OH)) (9CI) (CA INDEX NAME)

Cs-OH

RN 340154-98-5 HCAPLUS
 CN D-Mannose, 2-deoxy-4-O-(4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl)-2-(sulfoamino)-, 6-(hydrogen sulfate), tetrasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



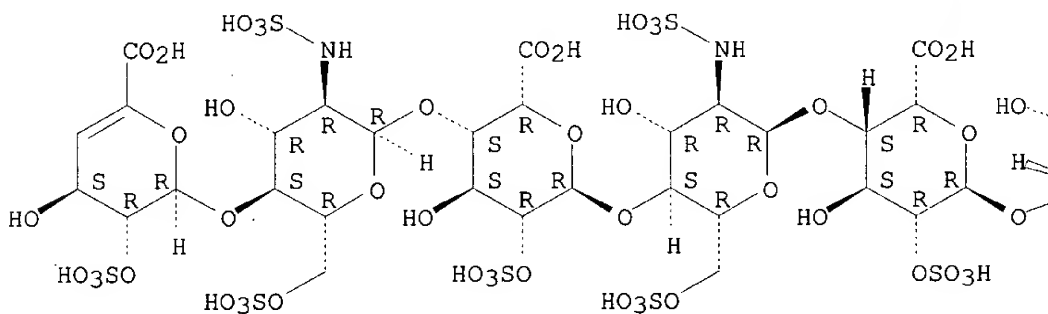
● 4 Na

RN 340156-51-6 HCAPLUS

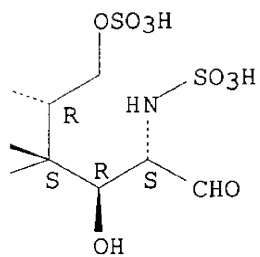
CN D-Mannose, O-4-deoxy-2-O-sulfo-.alpha.-L-threo-hex-4-enopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-O-2-deoxy-6-O-sulfo-2-(sulfoamino)-.alpha.-D-glucopyranosyl-(1.fwdarw.4)-O-2-O-sulfo-.alpha.-L-idopyranuronosyl-(1.fwdarw.4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), dodecasodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



● 12 Na



=> d ibib abs hitstr 3

L12 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:699358 HCAPLUS

DOCUMENT NUMBER: 125:316100

TITLE: A proposed model to monitor **heparin** therapy using the concentrated thrombin time which allows standardization of reagents and improved estimation of **heparin** concentrations

AUTHOR(S): Ray, M. J.; **Perrin, E. J.**; Smith, I. R.;
Hawson, G. A. T.

CORPORATE SOURCE: Departments Haematology and Physical Sciences, Prince Charles Hospital, Brisbane, 4032, Australia

SOURCE: Blood Coagulation Fibrinolysis (1996), 7(5), 515-521
CODEN: BLFIE7; ISSN: 0957-5235

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The concd. thrombin time (CTT), a thrombin time performed with a high concn. of thrombin, was evaluated as an alternative to the activated partial thromboplastin time (APTT) for monitoring of **heparin** therapy. Forty-nine plasmas from patients receiving unfractionated **heparin** therapy were tested. It was first demonstrated that CTTs using three com. reagents could be standardized against CTTs performed with a ref. reagent, MRC reagent 66/305. For comparison, APTTs were performed on the plasmas. As a benchmark of the degree of heparinization, the **heparin** concn. of the plasmas was detd. by chromogenic anti-IIa **heparin** assays, therapeutic range being 0.2-0.4 units/mL. The optimal relationships of the CTTs and APTT with the **heparin** concn. were established. These were used to predict the **heparin** concns. of the plasmas from the results of the APTT, CTT performed with the ref. reagent, and transformed CTT performed with each of the three com. reagents. In predicting the assayed plasma **heparin** concns., the accuracy of the APTT was only 53%, while the CTT was from 78 to 82%. The CTT can be standardized and, subject to results of clin. trials, could provide an improved method of monitoring **heparin** therapy.

IT 9002-04-4, Thrombin

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(concd. thrombin time; improved method of monitoring **heparin** therapy)

RN 9002-04-4 HCAPLUS

CN Thrombin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 9005-49-6, **Heparin**, biological studies

RL: BOC (Biological occurrence); BPR (Biological process); THU
(Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC
(Process); USES (Uses)
(improved method of monitoring **heparin** therapy)

RN 9005-49-6 HCAPLUS

CN **Heparin** (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 4

L12 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:1984 HCAPLUS

DOCUMENT NUMBER: 112:1984

TITLE: Production in Escherichia coli of a biologically active subfragment of von Willebrand factor corresponding to the platelet glycoprotein Ib, collagen and **heparin** binding domains

AUTHOR(S): Pietu, Genevieve; Meulien, Pierre; Cherel, Ghislaine; **Diaz, Joseph**; Baruch, Dominique; Courtney, Michael; Meyer, Dominique

CORPORATE SOURCE: Hop. Bicetre, Le Kremlin Bicetre, 94275, Fr.

SOURCE: Biochem. Biophys. Res. Commun. (1989), 164(3), 1339-47
CODEN: BBRCA9; ISSN: 0006-291X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A full-length cDNA for von Willebrand factor (vWF) has been cloned from a human lung cDNA library and a fragment of this cDNA has been modified to allow its expression in E. coli. This fragment, which corresponds to Val 449-Asn 730 of vWF and includes the glycoprotein Ib-binding domain and binding sites for collagen and **heparin**, was subcloned into an expression vector contg. an inducible .lambda. PL promoter. On induction, the expressed recombinant vWF subfragment migrated with a mol. wt. of around 38,000 after SDS-PAGE. It was identified as a vWF fragment by Western blotting using either a polyclonal or a monoclonal antibody which inhibits the binding of vWF to glycoprotein Ib. Following solubilization in urea, the bacterial ext. inhibited ristocetin-induced platelet aggregation and bound to ristocetin-treated platelets, to collagen, and to **heparin**.

IT 109319-16-6

RL: PRP (Properties)

(human gene for, cloning and expression in Escherichia coli of)

RN 109319-16-6 HCAPLUS

CN Blood-coagulation factor VIII, von Willebrand's (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 1

L73 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1995:576413 HCAPLUS
 DOCUMENT NUMBER: 122:293800
 TITLE: Preparing purified heparin fractions with low nitroso
 compound contents for use in pharmaceutical
 compositions
 INVENTOR(S): Branellec, Jean-Francois; Espejo, Jose; Picart,
 Philippe
 PATENT ASSIGNEE(S): Choay S.A., Fr.
 SOURCE: Eur. Pat. Appl., 14 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|-------------------------|------------------|----------|
| EP 623629 | A1 | 19941109 | EP 1994-400994 | 19940506 |
| EP 623629 | B1 | 19960821 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| FR 2704861 | A1 | 19941110 | FR 1993-5534 | 19930507 |
| FR 2704861 | B1 | 19950728 | | |
| CA 2122930 | AA | 19941108 | CA 1994-2122930 | 19940505 |
| AU 9461912 | A1 | 19941110 | AU 1994-61912 | 19940505 |
| AU 672291 | B2 | 19960926 | | |
| FI 9402095 | A | 19941108 | FI 1994-2095 | 19940506 |
| NO 9401686 | A | 19941108 | NO 1994-1686 | 19940506 |
| BR 9401920 | A | 19941129 | BR 1994-1920 | 19940506 |
| ZA 9403152 | A | 19950109 | ZA 1994-3152 | 19940506 |
| HU 70553 | A2 | 19951030 | HU 1994-1446 | 19940506 |
| AT 141618 | E | 19960915 | AT 1994-400994 | 19940506 |
| ES 2093494 | T3 | 19961216 | ES 1994-400994 | 19940506 |
| US 5599801 | A | 19970204 | US 1994-239320 | 19940506 |
| IL 109587 | A1 | 19970415 | IL 1994-109587 | 19940506 |
| RU 2133253 | C1 | 19990720 | RU 1994-15595 | 19940506 |
| PL 178294 | B1 | 20000428 | PL 1994-303336 | 19940506 |
| CZ 287889 | B6 | 20010314 | CZ 1994-1132 | 19940506 |
| CN 1096034 | A | 19941207 | CN 1994-105382 | 19940507 |
| CN 1066155 | B | 20010523 | | |
| TW 438812 | B | 20010607 | TW 1994-83104157 | 19940507 |
| JP 07126302 | A2 | 19950516 | JP 1994-95337 | 19940509 |
| PRIORITY APPLN. INFO.: | | FR 1993-5534 A 19930507 | | |

AB The title fractions, with nitroso compd. content .ltoreq.500 ppb, are
 prepd. by **depolymer.** with HNO₂. A 10.3% aq. soln. (pH 2.5) of 20
 kg Na heparin was stirred with 572 g NaNO₂ and sufficient HCl to maintain
 a pH of 2.5 until reaction was complete, adjusted to pH 10, stirred with
 200 g NaBH₄ for 15 h, acidified to pH 3.5-4, fractionated by pptn. with
 EtOH, treated with UV light (254 nm) for 9 min, purified by chromatog. on
 an anion exchanger, and treated with CaCl₂ to give Ca heparin contg. 53
 ppb nitroso compds.; vs. 3150 without UV treatment.

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L73 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2002 ACS
 IC ICM C08B037-10
 CC 44-5 (Industrial Carbohydrates)

Section cross-reference(s): 63

ST heparin fractionated nitroso compd **removal**; UV photolysis
nitroso compd heparin; pharmaceutical heparin purifn; nitrous acid
depolymerization

IT Ultraviolet radiation
(nitroso compd. **removal** by, from heparin fractions)

IT **Depolymerization**
(of **heparin** by nitrous acid, purifn. in)

IT Pharmaceuticals
(prepg. purified heparin fractions with low nitroso compd. contents for
use in pharmaceutical compns.)

IT Nitroso compounds
RL: REM (Removal or disposal); PROC (Process)
(**removal** of, from heparin fractions by UV light)

IT 7782-77-6, Nitrous acid
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(**depolymerization** of **heparin** in presence of, purifn. in)

IT 9041-08-1P, **Heparin sodium** salt 37270-89-6P, Heparin
calcium salt
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)
(prepg. purified **heparin** fractions with low nitroso compd.
contents for use in pharmaceutical compns.)

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L73 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:183690 HCAPLUS

DOCUMENT NUMBER: 118:183690

TITLE: Preparation of affinity-fractionated, heparin-derived oligosaccharides and their effects on selected biological activities mediated by **basic** fibroblast growth factor

AUTHOR(S): Ishihara, Masayuki; Tyrrell, David J.; Stauber, Gregory B.; Brown, Suzy; Cousens, Lawrence S.; Stack, Robert J.

CORPORATE SOURCE: Glycomed Incorp., Alameda, CA, 94501, USA

SOURCE: J. Biol. Chem. (1993), 268(7), 4675-83

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Homogeneously sized, heparin-derived oligosaccharides were prep'd. from **heparin** following partial **depolymer.** with nitrous acid, redn. with **sodium** borohydride, and fractionation by gel permeation chromatog. The resulting pools of di-, tetra-, hexa-, octa-, and decasaccharides were sequentially applied to an affinity column of human recombinant **basic** fibroblast growth factor (bFGF) covalently attached to Sepharose 4B and further fractionated into subpools based on their elution from this column in response to gradients of **sodium** chloride. The homogeneously sized pools and affinity-fractionated subpools of heparin-derived oligosaccharides were quant. assessed as inhibitors or enhancers of specific bFGF-mediated biol. activities in five sep. assay systems as follows: assay 1, competition with human lymphoblastoid cells expressing syndecan (RO-12 UC cells) for binding to bFGF-coated wells; assay 2, inhibition of 125I-bFGF binding to low-affinity sites of adrenocortical endothelial (ACE) cells; assay 3, inhibition of bFGF-induced proliferation of ACE cells; assay 4, support of mitogenic activity of bFGF in a growth stimulation assay of chlorate-treated ACE cells; and assay 5, enhancement of the in vitro interaction between 125I-bFGF and the recombinant extracellular domain of FGF high-affinity receptor. Heparin-derived hexa- and octasaccharides inhibited the interaction between cell surface heparan sulfate proteoglycan and bFGF (assays 1 and 2) and bFGF-induced proliferation of ACE cells (assay 3), but they were unable to enhance the binding of bFGF to its high-affinity receptor in vitro (assay 5) or to support bFGF-induced mitogenesis in ACE cells (assay 4). These two activities required at least a decasaccharide with high affinity for bFGF.

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L73 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:108670 HCAPLUS

DOCUMENT NUMBER: 116:108670

TITLE: Preparation of mixed polysaccharide sulfates with low molecular weight

INVENTOR(S): Debrie, Roger

PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S. A., Fr.

SOURCE: Ger. Offen., 8 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|------|----------|-----------------|----------|
| DE 4121115 | A1 | 19920102 | DE 1991-4121115 | 19910626 |
| FR 2663639 | A1 | 19911227 | FR 1990-8013 | 19900626 |
| FR 2663639 | B1 | 19940318 | | |
| NL 9101049 | A | 19920116 | NL 1991-1049 | 19910618 |
| AU 9179288 | A1 | 19920102 | AU 1991-79288 | 19910624 |
| AU 643531 | B2 | 19931118 | | |
| GB 2245898 | A1 | 19920115 | GB 1991-13589 | 19910624 |
| GB 2245898 | B2 | 19931006 | | |
| IL 98604 | A1 | 19980815 | IL 1991-98604 | 19910624 |
| NO 9102485 | A | 19911227 | NO 1991-2485 | 19910625 |
| DK 9101243 | A | 19911227 | DK 1991-1243 | 19910625 |
| CA 2045433 | AA | 19911227 | CA 1991-2045433 | 19910625 |
| FI 9103101 | A | 19911227 | FI 1991-3101 | 19910625 |
| SE 9101957 | A | 19911227 | SE 1991-1957 | 19910625 |
| SE 506267 | C2 | 19971124 | | |
| HU 57796 | A2 | 19911230 | HU 1991-2122 | 19910625 |
| HU 210925 | B | 19950928 | | |
| ZA 9104869 | A | 19920429 | ZA 1991-4869 | 19910625 |
| JP 04226101 | A2 | 19920814 | JP 1991-179030 | 19910625 |
| ES 2036922 | A1 | 19930601 | ES 1991-1505 | 19910625 |
| ES 2036922 | B1 | 19940301 | | |
| CH 682236 | A | 19930813 | CH 1991-1884 | 19910625 |
| BE 1006827 | A3 | 19950103 | BE 1991-607 | 19910625 |
| US 5389618 | A | 19950214 | US 1993-92577 | 19930716 |

PRIORITY APPLN. INFO.:

FR 1990-8013 19900626

US 1991-721315 19910626

AB Sulfates of polysaccharides with the **basic** structure of those in heparin and mol. wt. less than that of heparin (9-20% with mol. wt. <2000, 5-20% with mol. wt. .gtoreq.8000, polydispersity 1.3-1.6) are prepd. The sulfates are useful in preventing venous thromboses after operations. Thus, heparin benzyl ester Na salt (degree of esterification 13.3%, prepd. from heparin benzethonium salt and PhCH₂Cl) was heated (10 g) in H₂O with 0.9 g NaOH at 62.degree. for 1.5 h, neutralized with HCl, concd., and mixed with MeOH to give a product with wt.-av. mol. wt. 3900, polydispersity 1.39, and anticoagulant activity 22.6 IU, contg. 20% chains with mol. wt. <2000 and 5.5% with mol. wt. >8000.

IT **81209-41-8DP, Heparin benzyl ester sodium salt, depolymd.**

RL: PREP (Preparation)

(antithrombotics, prepn. and activity of)

RN 81209-41-8 HCAPLUS

CN Heparin, phenylmethyl ester, sodium salt (9CI) (CA INDEX NAME)

CM 1

CRN 9005-49-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 100-51-6
CMF C7 H8 O

HO-CH₂-Ph

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L73 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2002 ACS

IC ICM C08B037-10

ICS C08L005-10; A61K031-725

CC 44-5 (Industrial Carbohydrates)

Section cross-reference(s): 63

ST benzyl ester **heparin depolymn**; **heparin**

depolymd anticoagulant; benzethonium heparinate benzylation

IT Anticoagulants and Antithrombotics

(**depolymd. heparin**, prepn. and activity of)

IT **81209-41-8DP**, Heparin benzyl ester **sodium**
salt, **depolymd**.

RL: PREP (Preparation)

(antithrombotics, prepn. and activity of)

IT 50732-58-6P, Heparin benzethonium salt

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(prepn. and benzylation of)

IT 100-44-7, Benzyl chloride, reactions

RL: RCT (Reactant)

(reaction of, with heparin benzethonium salt)

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L73 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:538565 HCAPLUS

DOCUMENT NUMBER: 115:138565

TITLE: Supersulfated heparins with high antithrombotic activity

INVENTOR(S): Conti, Renato; Casati, Paolo; Gorini, Maria Beatrice; Maggi, Antonio

PATENT ASSIGNEE(S): Iketon Farmaceutici S.r.l., Italy

SOURCE: Eur. Pat. Appl., 9 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 432537 | A2 | 19910619 | EP 1990-122309 | 19901122 |
| EP 432537 | A3 | 19911113 | | |
| EP 432537 | B1 | 19950125 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| JP 03210302 | A2 | 19910913 | JP 1990-315683 | 19901122 |
| ES 2068969 | T3 | 19950501 | ES 1990-122309 | 19901122 |
| US 5164378 | A | 19921117 | US 1990-618051 | 19901126 |
| | | | IT 1989-22504 | 19891124 |

PRIORITY APPLN. INFO.:

AB Treating heparin with oleum contg. 2-6% free sulfuric anhydride at -10 to +20.degree. gives the depolymd. title product having mol. wt. 2000-5000 and sulfation degree (s) 3.4-4.3. Thus, 50 g vacuum-dried Na heparinate was stirred with 400 mL of 4% SO3 oleum at 5.degree., after 5 min, raising gradually the temp. to 20.degree. and maintaining for 30 min, transferred to 5 L cold water and 30% NaOH soln. added to pH 5-9, and kept at 2-3.degree. overnight to give a sulfated heparin.

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L73 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:672 HCAPLUS

DOCUMENT NUMBER: 112:672

TITLE: Preparation of a low-molecular-weight heparin with antithrombotic activity

INVENTOR(S): Lopez Belmonte, Lorenzo

PATENT ASSIGNEE(S): Laboratorios Farmaceuticos Rovi S. A., Spain

SOURCE: Span., 5 pp.
CODEN: SPXXAD

DOCUMENT TYPE: Patent

LANGUAGE: Spanish

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| ES 2003197 | A6 | 19881016 | ES 1987-20 | 19870105 |
| EP 293539 | A2 | 19881207 | EP 1987-500051 | 19870722 |
| EP 293539 | A3 | 19890412 | | |
| EP 293539 | B1 | 19940608 | | |
| R: AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| AT 106901 | E | 19940615 | AT 1987-500051 | 19870722 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | ES 1987-20 | 19870105 |
| | | | EP 1987-500051 | 19870722 |

AB **Heparin** is **depolymerized** to a product of mol. wt. 2500-6000 by treating a quaternary ammonium salt of heparin with a quaternary ammonium **hydroxide** in a hydroxylated solvent at 10-60.degree., followed by optional treatment with NaBH₄ and KMnO₄. The product, isolated as the Na, Ca, or Mg salt, has long-lasting antithrombotic activity. Benzethonium heparinate was hydrolyzed with benzyltrimethylammonium **hydroxide** in CH₂Cl₂-MeOH at room temp.; after addn. of Triton B, the product was pptd. with 10% NaOAc in MeOH. The product had a mol. wt. of 6000, an anti-Factor Xa activity of 140 units/mg, an anticoagulant activity of 65 USP units/mg, an ED₅₀ of 0.20 mg/kg in rats, and an LD₅₀ of >1600 mg/kg i.v. in rats.

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L73 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2002 ACS

IC ICM C08B037-10

CC 1-8 (Pharmacology)

Section cross-reference(s): 44

ST **heparin depolymerized** antithromboticIT Anticoagulants and Antithrombotics
(heparin hydrolysis products)IT Polymer degradation
(of heparin, in antithrombotic prepn.)IT Quaternary ammonium compounds, reactions
RL: RCT (Reactant)

(heparinates, hydrolysis of, in antithrombotic prepn.)

IT 100-85-6, Benzyltrimethylammonium **hydroxide**
RL: BIOL (Biological study)

(heparin hydrolysis with, in antithrombotic prepn.)

IT 9002-05-5, Blood-coagulation factor Xa
RL: PROC (Process)

(inhibition of, by heparin hydrolysis products)

- IT 9041-08-1P, Heparin **sodium** salt 37270-89-6P, Heparin calcium salt 54479-70-8P, Heparin magnesium salt
RL: SPN (Synthetic preparation); PREP (Preparation)
(low-mol.-wt., prepn. of, as antithrombotic)
- IT 9005-49-6DP, Heparin, hydrolysis products 50732-58-6DP, Benzethonium heparinate, hydrolysis products
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antithrombotics)

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L73 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1989:121368 HCAPLUS

DOCUMENT NUMBER: 110:121368

TITLE: Depolymerization of natural polyanions, such as nucleic acids and glycosaminoglycans

PATENT ASSIGNEE(S): Ajorca S. A., Argent.

SOURCE: Belg., 10 pp.
CODEN: BEXXAL

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|------|----------|-----------------|----------|
| BE 1000118 | A6 | 19880405 | BE 1987-861 | 19870804 |
| ES 2007373 | A6 | 19890616 | ES 1987-2175 | 19870724 |
| CH 678326 | A | 19910830 | CH 1987-2953 | 19870731 |
| SU 1639432 | A3 | 19910330 | SU 1987-4203197 | 19870803 |
| CN 87105497 | A | 19880413 | CN 1987-105497 | 19870805 |
| | | | AR 1986-304799 | 19860805 |

PRIORITY APPLN. INFO.:

AB The title process is carried out with **H2O2**, in the presence of Fe(II) salts, by a process involving formation of free radicals. Heparin Na (20 g) in 100 mL water was treated with 4 g Amberlite IR-120 (H+) followed by filtration. The filtrate (pH 4-4.5) was heated at 80.degree., with 4 mL 30% **H2O2** and 0.2 mL Fe(II) compd. soln. (1.5 g FeSO4.7H2O in 100 mL water). After 1 h the reaction was stopped with EtOH. The av. mol. wt. of the **depolymd. heparin** Na was 4.000, as compared to 12,000 for the starting product.

=> d ibib abs hitstr 7

L73 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1987:478204 HCAPLUS

DOCUMENT NUMBER: 107:78204

TITLE: Depolymerized hexosaminoglucan sulfates with antithrombotic, fibrinolytic, and antiinflammatory activity

INVENTOR(S): Mascellani, Giuseppe; Bianchini, Pietro

PATENT ASSIGNEE(S): Opocrin S.p.A., Italy

SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 8606729 | A1 | 19861120 | WO 1986-EP291 | 19860515 |
| W: AU, DK, HU, JP, NO, US | | | | |
| RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| DD 251355 | A5 | 19871111 | DD 1986-290192 | 19860513 |
| IL 78772 | A1 | 19910816 | IL 1986-78772 | 19860513 |
| AU 8659533 | A1 | 19861204 | AU 1986-59533 | 19860515 |
| AU 601910 | B2 | 19900920 | | |
| EP 221977 | A1 | 19870520 | EP 1986-903331 | 19860515 |
| EP 221977 | B1 | 19900808 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| JP 63500184 | T2 | 19880121 | JP 1986-503130 | 19860515 |
| JP 2510177 | B2 | 19960626 | | |
| HU 46028 | A2 | 19880928 | HU 1986-3344 | 19860515 |
| HU 203565 | B | 19910828 | | |
| AT 55396 | E | 19900815 | AT 1986-903331 | 19860515 |
| ZA 8603651 | A | 19870128 | ZA 1986-3651 | 19860516 |
| CA 1283098 | A1 | 19910416 | CA 1986-509396 | 19860516 |
| CN 86104301 | A | 19870304 | CN 1986-104301 | 19860517 |
| CN 1009096 | B | 19900808 | | |
| DK 8700157 | A | 19870113 | DK 1987-157 | 19870113 |
| DK 173804 | B1 | 20011105 | | |
| US 4973580 | A | 19901127 | US 1989-349706 | 19890510 |
| PRIORITY APPLN. INFO.: | | | IT 1985-20769 | A 19850517 |
| | | | EP 1986-903331 | A 19860515 |
| | | | WO 1986-EP291 | A 19860515 |
| | | | US 1987-6497 | B1 19870109 |

AB The title polysaccharides were prepd. by a free radical-initiated **depolymerization** of natural polysaccharides, such as **heparins**, heparan sulfates, dermatan sulfates, chondroitin sulfates, and hyaluronic acid in aq. soln. at 20-70.degree. using a **peroxide** selected from the group consisting of AcOOH, 3-ClC6H4C(O)OOH, **H2O2**, cumene hydroperoxide, Na2S2O8, and BzOOH, and a catalyst selected from Cu2+, Fe2+, Cr3+ and Cr2O72-. They are useful as antithrombotic, fibrinolytic and antiinflammatory agents with poor or no anticoagulant activity. Thus, 9% aq. **H2O2** was added with stirring at 35-60.degree. in 2.5 h to a soln. of 1 kg HFA 15 raw heparin, 0.495 kg NaCl, and 1 kg AcONa in 10 L H2O contg. 0.46 g Cu(OAc)2.H2O while holding the pH at 7.5 by addn. of 1N NaOH. The mixt. was successively treated with EDTA, AcOH, and MeOH to give a ppt. which was redissolved in H2O and again treated as described above to give 845.5 g heparin with mol. wt. of

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4600. This showed activated anti-factor X activity in vitro.

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L102 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:432654 HCAPLUS

DOCUMENT NUMBER: 133:37511

TITLE: Danaparoid sodium

AUTHOR(S): Acostamadiedo, Jose M.; Iyer, Uma G.; Owen, John

CORPORATE SOURCE: Wake Forest University School of Medicine,
Winston-Salem, NC, 27157, USA

SOURCE: Expert Opinion on Pharmacotherapy (2000), 1(4), 803-814

CODEN: EOPHF7; ISSN: 1465-6566

PUBLISHER: Ashley Publications Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 53 refs. Danaparoid **sodium** (Orgaran, Organon) is a **heparinoid glycosamino-glycuronan** antithrombotic agent approved for the prophylaxis of post-operative deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing elective hip replacement surgery. Danaparoid is a low **mol. wt.** heparinoid consisting of a mixt. of heparan sulfate (84%), dermatan sulfate (12%) and small amts. of chondroitin sulfate (4%), whose antithrombotic activity has been well established. Its pharmacol. effect is exerted primarily by inhibiting Factors **Xa** (FXa) and **IIa** (FIIa) at a ratio greater than heparin, with a minimal effect on platelet function. Danaparoid exhibits low cross-reactivity with heparin-induced antibodies when compared with heparin or low **mol. wt.** heparins (LMWH), thereby making it an excellent choice for the management of heparin-induced thrombocytopenia (HIT). It has excellent bioavailability following s.c. injection. Danaparoid has little effect on routine coagulation tests (activated partial thromboplastin time [aPTT], prothrombin time [PT], and thrombin time [TT]). Patients with elevated serum creatinine should be monitored carefully. For its FDA approved indication (DVT prophylaxis during hip replacement surgery), its cost per day is approx. eight times more than LMWH. Even though monitoring is not routinely necessary according to the manufacturer for its approved indication, monitoring is frequently necessary when it is used in other clin. scenarios. Its higher cost than comparable therapies for DVT prophylaxis and the low availability of the FXa assay in most non-tertiary care hospitals has limited the widespread use of danaparoid. Danaparoid has been found to be effective in the treatment of HIT although this is an off label use, despite being the most frequent reason why danaparoid is used.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L102 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:975757 HCAPLUS

DOCUMENT NUMBER: 123:350100

TITLE: Accelerated Stability Studies of Heparin

AUTHOR(S): Jandik, Kenneth A.; Kruep, Dale; Cartier, Michelle; Linhardt, and Robert J.

CORPORATE SOURCE: College of Pharmacy, University of Iowa, Iowa City, IA, 52242, USA

SOURCE: J. Pharm. Sci. (1996), 85(1), 45-51

CODEN: JPMSAE; ISSN: 0022-3549

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this study was to extend our understanding of the stability of heparin. **Sodium heparin**, derived from porcine intestinal mucosa, was first incubated in 0.1N HCl and 0.1N NaOH at 30 and 60.degree. and sampled at times ranging from 0 to 1000 h. The absorbance spectra of the products formed under basic conditions showed an UV maxima at 232 nm assocd. with chem. catalyzed .beta.-elimination at the **uronic** acid residues. The products formed under acidic conditions showed a decreased staining intensity consistent with desulfation and a decrease in **mol. wt.** corresponding to hydrolysis of glycosidic linkages when analyzed by gradient polyacrylamide gel electrophoresis. **Heparin** samples were next prepd. in 10 mM **sodium** phosphate buffer at pH 7.0 in sealed ampules that had been flushed with nitrogen and incubated at 100.degree.. Samples taken at times ranging from 0 to 4000 h were then analyzed. Heparin was relatively stable over the first 500 h, after which it rapidly degraded. Heparin, assayed using both anti-factor **Xa** and anti-factor **IIa** amidolytic methods retained 80-90% of its activity over the first 500 h, but these activities dropped precipitously, to .apprx.6% and .apprx.0.5% of the initial activity at 1000 h and 2000 h, resp. This rapid decompn. began only after the buffering capacity of the soln. was overwhelmed by acidic degradants, which caused the pH to decrease. Decompn. processes obsd. under these conditions included the endolytic hydrolysis of glycosidic linkages and loss of sulfation, particularly N-sulfate groups, and were similar to the degrdn. processes obsd. in 0.1N HCl. This study provides initial observations on heparin degrdn. pathways. More complete, quant. studies and studies leading to the isolation and characterization of specific degradants are still required.

=> d ibib abs hitstr 1

L79 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:599979 HCAPLUS

DOCUMENT NUMBER: 125:284766

TITLE: Bioactive **heparin** surfaces from
derivatization of polyacrylamide-grafted LLDPEAUTHOR(S): Wirsen, Anders; Ohrlander, Mattias; Albertsson,
Ann-ChristineCORPORATE SOURCE: Dep. of Polymer Technology, Royal Inst. of Technology,
Stockholm, S-100 44, Swed.

SOURCE: Biomaterials (1996), 17(19), 1881-1889

CODEN: BIMADU; ISSN: 0142-9612

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Primary amine groups were introduced into polyacrylamide-LLDPE films, using the Hofmann degrdn. synthesis. The Hofmann degrdn. was studied at room temp. using sodium hypochlorite and sodium **hydroxide** at different concns. Diazotized **heparin** was covalently bound to the grafted LLDPE film via the primary amine groups. Surfaces were analyzed with ESCA, ATR-IR, chloride titrn. and Toluidine Blue. Evaluation of the biol. activity of the **heparinized** surfaces was made by measuring the capacity for binding antithrombin (AT) and inhibition of the activated coagulation factor XII (FXIIa). The **heparinized** surfaces were able to bind up to 3 pmol cm⁻² of AT in soln. with ionic strengths of $I = 0.15$ and $I = 0.40$. No activation of the adsorbed FXII was detected.

IT **9005-49-6DP, Heparin**, reaction products with
polyacrylamide-grafted polyethylene
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(bioactive **heparin** surfaces from derivatization of
polyacrylamide-grafted LLDPE)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **9005-49-6, Heparin**, reactions

RL: RCT (Reactant)

(bioactive **heparin** surfaces from derivatization of
polyacrylamide-grafted LLDPE)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 2

L79 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:379939 HCAPLUS

DOCUMENT NUMBER: 122:196881

TITLE: Degradation behavior of ionic stepwise polyaddition polymers of medical interest

AUTHOR(S): Ferruti, P.; Ranucci, E.; Bignotti, F.; Sartore, L.; Bianciardi, P.; Marchisio, M. A.

CORPORATE SOURCE: Dip. Chim. Fis. Mater., Univ. Brescia, Brescia, 25123, Italy

SOURCE: J. Biomater. Sci., Polym. Ed. (1995), 6(9), 833-44

CODEN: JBSEEA; ISSN: 0920-5063

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Degradn. of poly(amidoamine)s (PAAs) and some other families of polymers structurally related to PAAs of medical interest are studied. PAAs are obtained by stepwise polyaddn. of primary monoamines, or bis secondary amines, to bisacrylamides. There are several other ter-amino polymers structurally related to PAAs, such poly(amido phosphine)s (PAPs), poly(ester-amine)s (PEAs), poly(ketone-amine)s (PKAs), poly(amidothioetheramine)s (PATAs) poly(ester-thioetheramine)s (PTEAs), and poly(sulfone thioetheramine)s (PSTAs). Most of the PAAs exhibit **heparin** complexing ability. PAAs are also being considered as sol. carriers for delivering anti-cancer drugs. Some of these polymers have been studied as antimicrobial agents. PAAs with different structures degrade at different rates under physiol. conditions. The degradn. rate is also strongly influenced by pH. The quaternized PATAs and PTEAs are reasonably stable over a period of some days, but ultimately degrade to oligomeric products, while the quaternized PAAs do rapidly degrade.

=> d ibib abs hitstr 3

L79 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1993:410731 HCAPLUS
 DOCUMENT NUMBER: 119:10731
 TITLE: Preparation of highly-sulfated **heparins**
 having improved antithrombotic activity
 INVENTOR(S): Nagasawa, Kinzo; Uchama, Hideki
 PATENT ASSIGNEE(S): Terumo Corp, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----|---|------|----------|-----------------|----------|
| | JP 05032703 | A2 | 19930209 | JP 1991-210096 | 19910726 |
| AB | The title heparins are prepd. by heating the solid state or dispersion in a stabilized medium of salts between heparin and an arom. heterocyclic base to effect the intramol. migration of N-sulfate groups onto OH groups, and further sulfating the sulfate-depleted amino groups, followed by depolymn. of the substrate and/or fractionation to yield the low mol. wt. fractions. A heparin -pyridinium salt was prepd., desiccated with P2O5, heated 90 min at 90.degree., cooled, solubilized in water, sulfated, and depolymd. | | | | |
| IT | 9005-49-6DP, Heparin , N-sulfated and partially depolymd. RL: PREP (Preparation) (antithrombotic, manuf. of) | | | | |
| RN | 9005-49-6 HCAPLUS | | | | |
| CN | Heparin (8CI, 9CI) (CA INDEX NAME) | | | | |

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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L79 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
 IC ICM C08B037-10
 ICA A61K031-725
 CC 44-5 (Industrial Carbohydrates)
 Section cross-reference(s): 63
 ST antithrombotic sulfated **heparin** low mol wt
 IT **Depolymerization**
 (of **heparins** after N-sulfation, for antithrombotic agents)
 IT Sulfation
 (of N-position heat-induced intramol. sulfonyl-rearranged **heparin**, for antithrombotic agents)
 IT Anticoagulants and Antithrombotics
 (N-sulfated **heparins** for, low mol. wt.)
 IT Rearrangement
 (intramol., thermal, of sulfonyl groups of **heparins**, followed by N-sulfation and depolymn.)
 IT **9005-49-6DP, Heparin**, N-sulfated and partially depolymd.
 RL: PREP (Preparation)
 (antithrombotic, manuf. of)
 IT 75803-60-0

KRISHNAN 09/909,797

RL: RCT (Reactant)
(heating and N-sulfation of, for manuf. of antithrombotic agents)

=> d ibib abs hitstr 4

L79 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:187879 HCAPLUS

DOCUMENT NUMBER: 114:187879

TITLE: Depolymerization of quarternary salts of
heparin for use as antithrombotics

INVENTOR(S): Lopez, Lorenzo L.

PATENT ASSIGNEE(S): Spain

SOURCE: U.S., 4 pp. Cont. of U.S. Ser. No. 212,568, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| US 4981955 | A | 19910101 | US 1990-485756 | 19900226 |
| PRIORITY APPLN. INFO.: | | | US 1988-212568 | 19880628 |

AB The title process uses quaternary ammonium **hydroxides**. A mixt. of 10 g benzetonium **heparinate** (I) in 50 mL CH₂Cl₂ with 2 mL 40% methanolic Triton B was allowed to settle for 24 h at room temp., mixed with 2 mL Triton B soln., and, after 24 h, mixed with 50 mL 10% methanolic AcONa to give 2.9 g depolymd. I with mol. wt. 6000, optical rotation +41.degree., S content 11.5%, N content 2.1, anti-Xa activity 140, and anticoagulant activity 65.

IT 50732-58-6DP, depolymd.

RL: PREP (Preparation)

(antithrombotic and anticoagulant, manuf. of)

RN 50732-58-6 HCAPLUS

CN Heparin, ion (neg.), N,N-dimethyl-N-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]benzenemethanaminium (9CI) (CA INDEX NAME)

CM 1

CRN 51053-42-0

CMF Unspecified

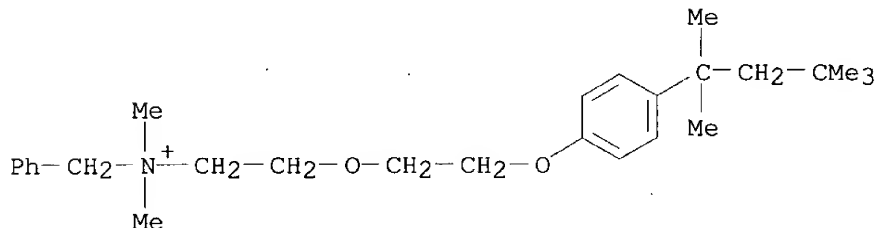
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 10172-60-8

CMF C27 H42 N O2



=> d ind 4

L79 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS
IC ICM C08B037-10
ICS C07H023-00; A61K031-725; A61K031-715
NCL 536021000
CC 44-5 (Industrial Carbohydrates)
Section cross-reference(s): 63
ST anticoagulant **heparin** depolymn; antithrombotic **heparin**
depolynd; benzetonium **heparinate** depolymn; quaternary ammonium
hydroxide depolymn
IT Anticoagulants and Antithrombotics
(depolynd. **heparins** as, prepn. of)
IT Quaternary ammonium compounds, uses and miscellaneous
RL: USES (Uses)
(**heparinates**, depolynd., antithrombotic and anticoagulant,
manuf. of)
IT Quaternary ammonium compounds, uses and miscellaneous
RL: USES (Uses)
(**hydroxides**, depolymn. of **heparins** in presence of)
IT **Depolymerization**
(reductive, of **heparin** quaternary ammonium salts, for
antithrombotics)
IT **50732-58-6DP**, depolynd.
RL: PREP (Preparation)
(antithrombotic and anticoagulant, manuf. of)
IT 100-85-6, Triton B
RL: PROC (Process)
(depolymn. of **heparins** in presence of)

=> d ibib abs hitstr 1

L86 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:565113 HCAPLUS

DOCUMENT NUMBER: 135:147424

TITLE: Derivatives of partially desulfated glycosaminoglycans endowed with antiangiogenic activity and devoid of anticoagulating effect, and process for their preparation

INVENTOR(S): Casu, Benito; Torri, Giangiacomo; Naggi, Anna Maria; Giannini, Giuseppe; Pisano, Claudio; Penco, Sergio

PATENT ASSIGNEE(S): Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., Italy

SOURCE: PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2001055221 | A1 | 20010802 | WO 2001-IT34 | 20010124 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: IT 2000-RM41 A 20000125

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Partially desulfated glycosaminoglycan derivs. are described, particularly heparin, and more particularly I [U = Q1-Q4 (X, X' = aldehyde, CH2D (D = OH, amino acid, peptide, carbohydrate residue, oligosaccharide residue)); R, R1 = SO3, acetyl; n, m = 1-40 (n+m = 6-40; m:n ratio = 10:2-1:1; zig-zag-like symbol indicates that the units marked m and n are statistically distributed along polysaccharide chain and not necessarily in sequence)]. The glycosaminoglycan derivs. have antiangiogenic activity and are devoid of anticoagulant activity. A process for prepg. the derivs. of the invention is also provided.

IT 9005-49-6, Heparin, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study);

RACT (Reactant or reagent)

(partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 1

L86 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS
 IC C08B037-10; A61K031-726; A61K031-727; A61K031-715
 CC 1-8 (Pharmacology)
 Section cross-reference(s): 33
 ST angiogenesis inhibitor desulfated glycosaminoglycan prepn; heparin
 desulfated prepn angiogenesis inhibitor
 IT **Hydrolysis**
 (acid; partially desulfated glycosaminoglycan derivs. with
 antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT Artery
 (angioplasty, restenosis after; partially desulfated glycosaminoglycan
 derivs. with antiangiogenic activity and devoid of anticoagulating
 effect, and prepn. process)
 IT Artery
 (coronary, bypass surgery, restenosis after; partially desulfated
 glycosaminoglycan derivs. with antiangiogenic activity and devoid of
 anticoagulating effect, and prepn. process)
 IT Artery, disease
 (coronary, restenosis; partially desulfated glycosaminoglycan derivs.
 with antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT Eye, disease
 (diabetic retinopathy; partially desulfated glycosaminoglycan derivs.
 with antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT Functional groups
 (diol; partially desulfated glycosaminoglycan derivs. with
 antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT Blood vessel
 (endothelium; partially desulfated glycosaminoglycan derivs. with
 antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT **Hydrolysis**
 (enzymic; partially desulfated glycosaminoglycan derivs. with
 antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT Antitumor agents
 (metastasis; partially desulfated glycosaminoglycan derivs. with
 antiangiogenic activity and devoid of anticoagulating effect, and
 prepn. process)
 IT Angiogenesis inhibitors
 Antitumor agents
 Cell adhesion
 Drug delivery systems
 Epoxy group
 Formyl group
 Oxidation
 Psoriasis
 Reduction
 Ring opening
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic
 activity and devoid of anticoagulating effect, and prepn. process)
 IT Glycosaminoglycans, biological studies

- RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Uronic acids
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Oligosaccharides, preparation
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Functional groups
 (primary alc.; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Proliferation inhibition
 (proliferation inhibitors; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Artery, disease
 (restenosis; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Eye, disease
 (retrolental fibroplasia; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Sulfation
 (retrosulfation; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Oligosaccharides, preparation
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (tetrasaccharides, and octasaccharides; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT Fibroblast growth factor receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (type 1; partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 9041-08-1, **Sodium heparin** 352437-72-0 352437-73-1
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 9025-39-2, Heparinase 9055-04-3, Lyase 52227-76-6, Heparitinase
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); CAT (Catalyst use); BIOL (Biological study); USES (Uses)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 9005-49-6, Heparin, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **RCT (Reactant)**; BIOL (Biological study); RACT (Reactant or reagent)

- (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 53260-52-9P, Desulfated heparin
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 64859-64-9, N-Acetyl-N-desulfo heparin 196887-68-0, 2-O-Desulfated heparin 352437-74-2
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 685-73-4, Galacturonic acid 3402-98-0, Iduronic acid 3402-98-0D, Iduronic acid, unsatd. derivs. 4607-22-1, N-Sulfoglucosamine
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)
- IT 7790-28-5, Sodium periodate
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (partially desulfated glycosaminoglycan derivs. with antiangiogenic activity and devoid of anticoagulating effect, and prepn. process)

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L86 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:395643 HCAPLUS

DOCUMENT NUMBER: 133:26855

TITLE: Modified low-molecular-weight heparin that inhibits clot-associated coagulation factors

INVENTOR(S): Weitz, Jeffrey I.; Hirsh, Jack

PATENT ASSIGNEE(S): Hamilton Civic Hospitals Research Development Inc., Can.

SOURCE: U.S., 25 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------|------|----------|-----------------|----------|
| US 6075013 | A | 20000613 | US 1998-92325 | 19980605 |
| PRIORITY APPLN. INFO.: US 1998-72098P | | | P | 19980606 |

AB Comps. and methods are provided for the treatment of cardiovascular diseases. More particularly, the invention relates to modifying thrombus formation by administering an agent which, inter alia, is capable of (1) inactivating fluid-phase thrombin and thrombin which is bound either to fibrin in a clot or to some other surface by catalyzing antithrombin; and (2) inhibiting thrombin generation by catalyzing factor Xa inactivation by antithrombin III (ATIII). The comps. and methods of the invention are particularly useful for preventing thrombosis in the circuit of cardiac bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from thrombus-related cardiovascular conditions, e.g. unstable angina, acute myocardial infarction (heart attack), cerebrovascular accidents (stroke), pulmonary embolism, deep vein thrombosis, arterial thrombosis, etc.

IT **9005-49-6P**, Heparin, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); **RCT (Reactant)**; THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 2

L86 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS

IC ICM A61K031-725

NCL 514056000

CC 1-8 (Pharmacology)

Section cross-reference(s): 63

ST modified low mol wt heparin coagulation factor inhibition; antithrombotic
modified low mol wt heparin

- IT Thrombosis
(arterial; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Artery
(atherectomy, increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT **Hydrolysis**
(base, heparin limited periodate oxidn./**hydrolysis**; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Heart
(cardiac catheterization, increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Medical goods
(catheters, catheterization, increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Thrombosis
(coronary arterial; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Artery, disease
Artery, disease
(coronary, thrombosis; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Artery, disease
(coronary, thrombus due to; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Lung, disease
(embolism; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(exosite 2; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Oxidation
(heparin limited periodate oxidn./**hydrolysis**; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Cardiopulmonary bypass
(increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Drug delivery systems
(injections; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Allosterism
Anticoagulants
Blood coagulation
Drug delivery systems
Molecular association

(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT Fibrins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT Heart

(surgery, increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT Atherosclerosis

(thrombus due to; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT Thrombosis

(venous; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT 7790-28-5, Sodium periodate

RL: RCT (Reactant); RACT (Reactant or reagent)
(**heparin** limited periodate oxidn./**hydrolysis**;
modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT 8001-27-2, Hirudin 78768-79-3, Prothrombin fragment 2 121822-23-9, Hirugen

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT 9005-49-6P, Heparin, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); **RCT (Reactant)**; THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

IT 9000-94-6, Antithrombin 9002-04-4, Blood coagulation factor IIa 9002-05-5, Blood coagulation factor Xa

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

=> d ibib abs hitstr 3

L86 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:160928 HCAPLUS

DOCUMENT NUMBER: 112:160928

TITLE: Heparin derivatives for pharmaceuticals and process for their preparation

INVENTOR(S): Piani, Silvano; Tamagnone, Gianfranco; Alpino, Raul Roberto; Milani, Maria Rita; Fantuz, Marinella

PATENT ASSIGNEE(S): Alfa Wassermann S.p.A., Italy

SOURCE: Eur. Pat. Appl., 12 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 347588 | A1 | 19891227 | EP 1989-109030 | 19890519 |
| EP 347588 | B1 | 19940727 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| ES 2012748 | T3 | 19941016 | ES 1989-109030 | 19890519 |
| ZA 8903882 | A | 19900228 | ZA 1989-3882 | 19890523 |
| AU 8935128 | A1 | 19891214 | AU 1989-35128 | 19890524 |
| AU 611028 | B2 | 19910530 | | |
| US 5010063 | A | 19910423 | US 1989-357548 | 19890526 |
| IL 90411 | A1 | 19930513 | IL 1989-90411 | 19890526 |
| DK 8902850 | A | 19891211 | DK 1989-2850 | 19890609 |
| DK 173818 | B1 | 20011119 | | |
| FI 8902850 | A | 19891211 | FI 1989-2850 | 19890609 |
| FI 94534 | B | 19950615 | | |
| FI 94534 | C | 19950925 | | |
| NO 8902366 | A | 19891211 | NO 1989-2366 | 19890609 |
| NO 174259 | B | 19931227 | | |
| NO 174259 | C | 19940406 | | |
| JP 02064102 | A2 | 19900305 | JP 1989-148211 | 19890609 |
| JP 07039442 | B4 | 19950501 | | |
| CA 1309402 | A1 | 19921027 | CA 1989-602338 | 19890609 |

PRIORITY APPLN. INFO.: IT 1988-3504 A 19880610

AB Title derivs., having antithrombotic activity and reduced hemorrhagic and anticoagulant effects, are prepd. by treating heparins in a basic medium, optionally in the presence of alkali metal salts and a reducing agent. The derivs. exhibit C-13 NMR shifts at 53 and 54 ppm and a sp. rotation ([.alpha.]D20) of +50.degree. to +90.degree.. A purified heparin (S 10.56%, sulfate-COOH ratio 2.20, [.alpha.]D20 +47.degree.) (1.8 g) was heated in 45 mL H2O contg. NaOH 0.4, NaOAc 2.38 and NaBH4 0.01 g at 60.degree. for 3.5 h to give a deriv.

IT 9005-49-6, Heparin, reactions

RL: RCT (Reactant)

(modification of, for antithrombotic agents)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ind 3

L86 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS
 IC ICM C08B037-10
 ICS A61K031-725
 CC 44-5 (Industrial Carbohydrates)
 Section cross-reference(s): 63
 ST antithrombotic heparin deriv prepn; alkali **hydrolysis** heparin
 deriv antithrombotic; redn agent heparin deriv antithrombotic
 IT Reducing agents
 Bases, biological studies
 Chlorides, biological studies
 Salts, biological studies
 Sulfates, biological studies
 RL: BIOL (Biological study)
 (heparin treatment by, in manuf. of antithrombotic agents)
 IT 10043-52-4, Calcium chloride, biological studies 10361-37-2, Barium
 chloride, biological studies 16940-66-2, **Sodium** borohydride
 (NaBH4) 62-54-4, Calcium acetate 127-08-2, Potassium acetate
 127-09-3, **Sodium** acetate 142-72-3, Magnesium acetate
 543-80-6, Barium acetate 1310-73-2, **Sodium** hydroxide,
 biological studies 7447-40-7, Potassium chloride, biological studies
 7487-88-9, Magnesium sulfate, biological studies 7647-14-5,
Sodium chloride, biological studies 7757-82-6, **Sodium**
 sulfate, biological studies 7778-80-5, Potassium sulfate, biological
 studies 7786-30-3, Magnesium chloride, biological studies
 RL: BIOL (Biological study)
 (heparin treatment by, in manuf. of antithrombotic agents)
 IT 9041-08-1, **Sodium heparin**
 RL: PROC (Process)
 (modification of, for antithrombotic agents)
 IT 9005-49-6, Heparin, reactions
 RL: RCT (Reactant)
 (modification of, for antithrombotic agents)
 IT 9005-49-6DP, Heparin, **hydrolyzed**, reduced 9041-08-1DP,
Sodium heparin, hydrolyzed, reduced
 RL: PREP (Preparation)
 (prepn. of, as antithrombotic agents)

Priority 7/21/2000

KRISHNAN 09/909,797

=> d ibib abs hitstr 1

L103 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:199745 HCAPLUS
DOCUMENT NUMBER: 136:318708
TITLE: Reviparin **sodium** - a new low
molecular weight heparin
AUTHOR(S): Breddin, Hans Klaus
CORPORATE SOURCE: International Institute of Thrombosis and Vascular
Diseases e. V., Frankfurt/Main, Germany
SOURCE: Expert Opinion on Pharmacotherapy (2002), 3(2), ←
173-182
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Reviparin **sodium** (Clivarine, Knoll AG) is a low
mol. wt. heparin (LMWH) with a mean peak
mol. wt. of 3900 Da. It is characterized by a narrow
mol. wt. distribution profile, with an anti-factor
Xa (anti-Xa):anti-factor IIa (
anti-IIa) ratio of .gtoreq. 3.6. In healthy human
volunteers, plasma **anti-Xa** activity was up to five
times higher and lasted three times longer with reviparin compared with
unfractionated heparin (UFH). Unlike UFH, reviparin has negligible
effects on global clotting tests. Reviparin has been shown to be as
effective as UFH in different prophylactic indications and causes fewer
injection-site hematomas. At a daily dose of 1750 IU **anti-**
Xa it was as effective as UFH in preventing deep vein thrombosis
(DVT) in moderate risk surgery (general and abdominal) and significantly
reduced DVT in patients with brace immobilization of the legs. At a daily
dose of 4200 IU **anti-Xa** reviparin was as effective as
UFH or enoxaparin in preventing DVT in high risk orthopedic surgery and as
effective as UFH in prevention of DVT and/or pulmonary embolism (PE)
and/or mortality in high risk orthopedic surgery. In patients with acute
venous thromboembolism (VTE), reviparin was more effective than UFH in
thrombus redn. and at least as effective as UFH in the prevention of clin.
recurrence of DVT and/or PE. The use of reviparin is assocd. with a
similar or lower incidence of bleeding complications than UFH.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L103 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:715791 HCAPLUS

DOCUMENT NUMBER: 136:379763

TITLE: Pharmacodynamics of intravenous and subcutaneous tinzaparin and heparin in healthy volunteers

AUTHOR(S): Fossler, Michael J.; Barrett, Jeffrey S.; Hainer, James W.; Riddle, J. G.; Ostergaard, Per; Van Der Elst, Eric; Sprogel, Per

CORPORATE SOURCE: Clinical Pharmacokinetics, DuPont Pharmaceuticals, Wilmington, DE, USA

SOURCE: American Journal of Health-System Pharmacy (2001), 58(17), 1614-1621

CODEN: AHSPEK; ISSN: 1079-2082

PUBLISHER: American Society of Health-System Pharmacists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacodynamics of i.v. and s.c. tinzaparin **sodium** compared with **heparin** in healthy volunteers were studied. A randomized, open-label, five-treatment, five-period-crossover study with a Latin square design was performed in 30 healthy men to est. tinzaparin pharmacodynamics (**anti-Xa** and **anti-IIa** activities) after single-dose i.v. and s.c. administration, to evaluate abs. bioavailability, to det. the effect of a preservative (benzyl alc.), to evaluate the dose-activity relationship, and to compare tinzaparin with unfractionated heparin. Treatments were (1) heparin 5,000 units s.c., (2) tinzaparin 4,500 **anti-Xa** IU without preservative s.c., (3) tinzaparin 4,500 **anti-Xa** IU without preservative i.v., (4) tinzaparin 12,250 **anti-Xa** IU with preservative s.c., and (5) tinzaparin 4,500 **anti-Xa** IU with preservative s.c. Blood samples for the measurement of **anti-Xa** and **anti-IIa** activities were drawn over 24 h. **Anti-Xa** and **anti-IIa** activities were detd. by chromogenic methods; data were analyzed by using a noncompartmental approach. The clearance of tinzaparin based on **anti-Xa** activity ranged from 1.14 to 2.04 L/h. The vol. of distribution was 3.1-5.0 L, suggesting that the mol. entities responsible for **anti-Xa** and **anti-IIa** activities are confined to the intravascular space. Mean peak **anti-Xa** activity occurred three to four hours after s.c. injection, independent of the dose. The mean half-life of **anti-Xa** activity after s.c. injection ranged from 3.41 to 4.13 h and was independent of the dose. The mean abs. bioavailability of s.c. tinzaparin was 86.7%. Intersubject pharmacodynamic variability was low for tinzaparin compared with heparin. Benzyl alc. did not affect tinzaparin pharmacodynamics. A clear dose-activity relationship was seen for the two fixed doses of tinzaparin (12,250 and 4,500 IU). Single doses of tinzaparin were safe and well tolerated after administration by either route. The **anti-Xa** profile of tinzaparin supports the pharmacodynamic superiority of low-mol.-wt. heparins over std. i.v. heparin administration. This pharmacodynamic study in healthy volunteers indicates that s.c. tinzaparin sodium was well absorbed; the presence of a preservative, benzyl alc., did not affect the activity of tinzaparin; and tinzaparin activity is dose-related.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

KRISHNAN 09/909,797

=> d ibib abs hitstr 3

L103 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:606695 HCAPLUS

DOCUMENT NUMBER: 135:326881

TITLE: Reviparin: A review of its efficacy in the prevention and treatment of venous thromboembolism

AUTHOR(S): Wellington, Keri; McClellan, Karen; Jarvis, Blair

CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.

SOURCE: Drugs (2001), 61(8), 1185-1209

CODEN: DRUGAY; ISSN: 0012-6667

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with refs. Reviparin (reviparin **sodium**) is a low mol. wt. **heparin** (LMWH) that catalyzes the inactivation of factors **Xa** and **IIa** by binding to antithrombin, which ultimately leads to the inhibition of the clotting cascade. It is administered s.c. Reviparin 7000 to 12,600 anti-XaIU/day was found to be as effective as i.v. unfractionated heparin in preventing the clin. recurrence of acute deep vein thrombosis (DVT) and/or pulmonary embolism in 1 large randomized, multicenter trial (COLUMBUS) and was significantly more effective than i.v. unfractionated heparin in the prevention of recurrent venous thromboembolism in another large randomized, multicenter trial (CORTES). Reviparin has also been compared with unfractionated heparin in children with established DVT. However, the trial was under-powered and no conclusion could be made regarding comparative efficacy. As prophylaxis, reviparin 1750 anti-XaIU once daily was as effective as unfractionated **heparin** 5000 IU twice daily in 1311 patients undergoing abdominal surgery and, in a once daily dosage of 4200 anti-XaIU, was as effective as s.c. enoxaparin **sodium** 40 mg/day or acenocoumarol in patients undergoing hip replacement surgery. Reviparin 1750 anti-XaIU also effectively prevented DVT, compared with no treatment, in patients undergoing knee arthroscopy. It was also more effective than placebo in patients with brace immobilization of the lower extremity. Reviparin was compared with "std. care" in children with central venous lines. However, the trial was too small to make conclusions regarding its efficacy. Comparative data indicate that reviparin is at least as well tolerated as **heparin** and enoxaparin **sodium**. However, in a large (n = 1279) trial there were significantly fewer major bleeding episodes in patients receiving reviparin than in patients given the oral anticoagulant acenocoumarol. The most commonly reported adverse events in therapeutic trials have been intraoperative blood loss and postoperative bleeding complications such as wound hematoma, bruising and injection site hemorrhage. Reviparin was also well tolerated in 2 studies in children aged .1toeq.16 yr. Reviparin has shown efficacy in the treatment of established DVT and in the prevention of postoperative DVT after moderate and high risk surgery and was as effective as enoxaparin sodium or acenocoumarol in patients undergoing hip replacement surgery. As an effective and well tolerated antithrombotic agent, reviparin is likely to assume a significant role in the treatment and prevention of DVT, as it appears to have a preferable tolerability profile to s.c. heparin after moderate risk surgery and is at least as effective as i.v. heparin in the treatment of established DVT.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 4

L103 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:181817 HCAPLUS

DOCUMENT NUMBER: 134:361172

TITLE: Anticoagulant Pharmacodynamics of Tinzaparin Following 175 IU/kg Subcutaneous Administration to Healthy Volunteers

AUTHOR(S): Barrett, J. S.; Hainer, J. W.; Kornhauser, D. M.; Gaskill, J. L.; Hua, T. A.; Sprogel, P.; Johansen, K.; van Lier, J. J.; Knebel, W.; Pieniaszek, H. J.

CORPORATE SOURCE: DuPont Pharmaceuticals, Wilmington, Newark, DE, 19714, USA

SOURCE: Thrombosis Research (2001), 101(4), 243-254 *adonis?* X
CODEN: THBRAA; ISSN: 0049-3848

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tinzaparin, a **sodium** salt of a low-mol.-wt.

heparin (LMWH) produced via **heparinase** digestion, is used for the treatment of deep vein thrombosis (DVT) and pulmonary embolism in conjunction with warfarin for the prevention of DVT in patients undergoing hip or knee replacement surgery, and as an anticoagulant in hemodialysis circuits. Its av. **mol. wt** ranges between 5500 and 7500 daltons (Da); the percentage of chains with **mol. wt**: lower than 2000 Da is not more than 10% in the marketed tinzaparin formulation. While this fraction is generally considered pharmacol. inactive, this has never been evaluated in vivo. The importance of the <2000 Da fraction on the anticoagulant pharmacodynamics of tinzaparin assessed by **anti-Xa** and **anti-IIa** activity was studied in a two-way crossover trial. In this trial, 30 healthy volunteers received a single 175 IU/kg s.c. administration of tinzaparin contg. approx. 3.5% of the <2000 Da fraction and a tinzaparin-like LMWH contg. 18.3% of the <2000 Da fraction. The **anti-Xa/anti-IIa** ratios of the drug substances were comparable at 1.5 and 1.7 for tinzaparin and the tinzaparin-like LMWH, resp. Both formulations were safe and well tolerated. Mean max. plasma **anti-Xa** activity (Amax) was approx. 0.818 IU/mL at 4 h following tinzaparin injection. Mean max. plasma **anti-IIa** activity was 0.308 IU/mL at 5 h postdose. Intersubject variation was lower (<18% for both **anti-Xa** and **anti-IIa** metrics) than in previous fixed-dose administration studies. There was no correlation between **anti-Xa** or **anti-IIa** AUC or Amax and bodyweight in the present study supporting the wt.-adjusted dosing regimen. Individual **anti-Xa** and **anti-IIa** profiles following the single 175 IU/kg s.c. administration of the tinzaparin-like LMWH were similar to that obtained with tinzaparin. Based on av. equivalence criteria, the two LMWH preps. were detd. to be bioequivalent using either **anti-Xa** or **anti-IIa** activity as biomarkers. The calcd. intrasubject variabilities were low (<14% for **anti-Xa** activity and <18% for **anti-IIa** activity) yielding little evidence for a significant Subject.times.Formulation interaction. In summary, **anti-Xa** and **anti-IIa** activity following a single s.c. administration of tinzaparin 175 IU/kg to healthy volunteers yielded activity consistent with targeted therapeutic levels derived from previous trials in adult DVT patients. Wt.-based dosing for the treatment of DVT appears rational based on the redn. in **anti**

-Xa and anti-IIa variability consistent with the recommendation derived from earlier fixed-dose pharmacokinetic studies. Furthermore, differences in the percentage of mols. in the <2000 Da mol. wt. fraction of tinzaparin do not translate into differences in anti-Xa and anti-IIa activity in vivo.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 5

L103 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:62347 HCAPLUS

DOCUMENT NUMBER: 134:120946

TITLE: Compositions comprising very low-molecular weight heparin

INVENTOR(S): Mardiguian, Jean

PATENT ASSIGNEE(S): Laboratorios Farmaceuticos Rovi, S.A., Spain

SOURCE: Eur. Pat. Appl., 11 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|-------------------|----------|-----------------|------------|
| EP 1070503 | A1 | 20010124 | EP 1999-500184 | 19991013 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| ES 2161615 | A1 | 20011201 | ES 1999-1671 | 19990723 |
| BR 9905820 | A | 20010313 | BR 1999-5820 | 19991028 |
| US 6384021 | B1 | 20020507 | US 1999-433409 | 19991103 |
| PRIORITY APPLN. INFO.: | | | ES 1999-1671 | A 19990723 |
| OTHER SOURCE(S): | MARPAT 134:120946 | | | |

AB The invention provides a compns. of heparins of very low -mol. wt. having specified formula. Such compns. of heparin are composed of mixts. of oligosaccharides or fragments of heparin and are characterized by having anti-Xa activity and anti-factor IIa activity and because they can be used as antithrombotic medicaments.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 6

L103 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:31543 HCAPLUS

DOCUMENT NUMBER: 134:105837

TITLE: Medium **molecular-weight** heparin
compositions that inhibit clot associated coagulation
factors for treatment of cardiovascular diseases

INVENTOR(S): Weitz, Jeffrey I.; Hirsh, Jack

PATENT ASSIGNEE(S): Hamilton Civic Hospitals Research Development, Inc.,
Can.

SOURCE: PCT Int. Appl., 82 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2001002443 | A1 | 20010111 | WO 2000-CA774 | 20000629 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| BR 2000012202 | A | 20020402 | BR 2000-12202 | 20000629 |
| EP 1192187 | A1 | 20020403 | EP 2000-941847 | 20000629 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |

PRIORITY APPLN. INFO.:

US 1999-141865P P 19990630

US 1999-154744P P 19990917

WO 2000-CA774 W 20000629

AB The present invention relates to modifying thrombus formation and growth by administering a medium **mol. wt.** heparin (MMWH) compn. that, inter alia, is capable of (1) inactivating fluid-phase thrombin as well as thrombin which is bound either to fibrin in a clot or to some other surface by catalyzing antithrombin; and (2) inhibiting thrombin generation by catalyzing factor **Xa** inactivation by antithrombin III (ATIII). In addn., the present invention provides methods and compns. useful for treating cardiovascular disease. The MMWH compns. have an antifactor **IIa** activity of .apprx.40-100 U/mg and an antifactor **Xa** activity of .apprx.90-150 U/mg.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 7

L103 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:709218 HCAPLUS

DOCUMENT NUMBER: 134:231459

TITLE: Comparative pharmacokinetics of LMWHs

AUTHOR(S): Samama, Meyer M.; Gerotziafas, Grigoris T.

CORPORATE SOURCE: Service d'Hematologie Biologique, Hopital Hotel-Dieu de Paris, Paris, 75181/04, Fr.

SOURCE: Seminars in Thrombosis and Hemostasis (2000), 26(Suppl. 1), 31-38

CODEN: STHMBV; ISSN: 0094-6176

PUBLISHER: Thieme Medical Publishers, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A variety of pharmaceutical prepn. of low-mol.-wt. heparins (LMWHs) are available. They belong to the same family of compds.-ie, heparin derivs. with a narrow distribution of mean mol. wts. (MWs). LMWHs have different methods of prepn., which result in variations in mean MW, distribution of MW, and pharmacokinetic (PK) and pharmacodynamic (PD) profiles. The mean MW of these compds. ranges from 3600 to 6500 daltons. The ratio of anti-Xa (aXa) and anti-IIa (aIIa) activities of the different LMWHs ranges from 1.5 to > 10. After s.c. (SC) injection of a prophylactic or therapeutic dose, the peak values for plasma aXa or aIIa activity may vary twofold to threefold because of differences in bioavailability, plasma clearance (Cl_{plasma}), and half-life (t_{1/2}). The injection of equiv. amts. of product, based on aXa and aIIa IU (IU), may result in different areas under the curve for the resp. activities. Although tinzaparin has a high aIIa specific activity per mg (and consequently, a low aXa/aIIa ratio), SC injection of 40 mg of enoxaparin (4000 aXa IU) results in a higher aXa peak value in patients with total hip replacement than 4500 aXa IU of tinzaparin. Differences in aIIa and aXa peak activities are more striking when high doses of LMWHs are used. The activated partial thromboplastin time (aPTT) can be significantly prolonged, an effect that is related to aIIa and aXa activity. The vol. of distribution of LMWHs is of the same order of magnitude as that of the plasma vol. The mean retention time of aXa activity varies from 5.2 (dalteparin) to .apprx.7 h (enoxaparin, nadroparin). Bioavailability of prophylactic doses of LMWHs ranges from 86% (dalteparin) to 98% (enoxaparin, nadroparin). PK parameters appear to be minimally affected by a patient's age. The Cl_{plasma} is different for each LMWH: 16 mL/min enoxaparin, 21 mL/min nadroparin, 33 mL/min dalteparin, 19 mL/min reviparin, and 22 mL/min tinzaparin. Accumulation of product has been obsd. for almost all LMWHs in patients with renal insufficiency. LMWHs are effective and safe for treatment or prophylaxis of venous thromboembolism during pregnancy, because they do not cross the placenta. No data are available regarding the passage of LMWHs into the milk in lactating women. Although LMWHs are also effective in prevention and treatment of thromboembolic disease in children, optimal use of these agents in pediatric patients has not been detd. In summary, the PD and PK of LMWHs have been well documented and have demonstrated that LMWHs have a more predictable response, a greater bioavailability, and a longer aXa t_{1/2} than unfractionated heparin. However, their distribution of MW affects their physicochem. and biol. properties, as well as PK characteristics. The concept of aXa/aIIa ratio (detd. in vitro) does not account for the differing PK of aXa and aIIa activity in circulating blood.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS

KRISHNAN 09/909,797

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 8

L103 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:395643 HCAPLUS
 DOCUMENT NUMBER: 133:26855
 TITLE: Modified low-molecular-weight
 heparin that inhibits clot-associated coagulation
 factors
 INVENTOR(S): Weitz, Jeffrey I.; Hirsh, Jack
 PATENT ASSIGNEE(S): Hamilton Civic Hospitals Research Development Inc.,
 Can.
 SOURCE: U.S., 25 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|------------|
| US 6075013 | A | 20000613 | US 1998-92325 | 19980605 |
| PRIORITY APPLN. INFO.: | | | US 1998-72098P | P 19980606 |

AB Comps. and methods are provided for the treatment of cardiovascular diseases. More particularly, the invention relates to modifying thrombus formation by administering an agent which, inter alia, is capable of (1) inactivating fluid-phase thrombin and thrombin which is bound either to fibrin in a clot or to some other surface by catalyzing antithrombin; and (2) inhibiting thrombin generation by catalyzing factor **Xa** inactivation by antithrombin III (ATIII). The comps. and methods of the invention are particularly useful for preventing thrombosis in the circuit of cardiac bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from thrombus-related cardiovascular conditions, e.g. unstable angina, acute myocardial infarction (heart attack), cerebrovascular accidents (stroke), pulmonary embolism, deep vein thrombosis, arterial thrombosis, etc.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 8

L103 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2002 ACS
 IC ICM A61K031-725
 NCL 514056000
 CC 1-8 (Pharmacology)
 Section cross-reference(s): 63
 ST modified low **mol wt** heparin coagulation factor
 inhibition; antithrombotic modified low **mol wt** heparin
 IT Thrombosis
 (arterial; modified low-**mol.-wt.** heparin for
 inhibition of clot-assocd. coagulation factors and prevention and
 treatment of thrombotic conditions)
 IT Artery
 (atherectomy, increased risk for thrombus in; modified low-**mol**
 .-**wt.** heparin for inhibition of clot-assocd. coagulation
 factors and prevention and treatment of thrombotic conditions)
 IT Hydrolysis
 (base, heparin limited periodate oxidn./hydrolysis; modified low-
mol.-wt. heparin for inhibition of clot-assocd.

- coagulation factors and prevention and treatment of thrombotic conditions)
- IT Heart
(cardiac catheterization, increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Medical goods
(catheters, catheterization, increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Thrombosis
(coronary arterial; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Artery, disease
Artery, disease
(coronary, thrombosis; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Artery, disease
(coronary, thrombus due to; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Lung, disease
(embolism; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(exosite 2; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Oxidation
(heparin limited periodate oxidn./hydrolysis; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Cardiopulmonary bypass
(increased risk for thrombus in; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Drug delivery systems
(injections; modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Allosterism
Anticoagulants
Blood coagulation
Drug delivery systems
Molecular association
(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Fibrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modified low-mol.-wt. heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of

- thrombotic conditions)
- IT Heart
(surgery, increased risk for thrombus in; modified low-**mol.-wt.** heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Atherosclerosis
(thrombus due to; modified low-**mol.-wt.** heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT Thrombosis
(venous; modified low-**mol.-wt.** heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT 7790-28-5, **Sodium** periodate
RL: RCT (Reactant); RACT (Reactant or reagent)
(**heparin** limited periodate oxidn./hydrolysis; modified low-**mol.-wt. heparin** for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT 8001-27-2, Hirudin 78768-79-3, Prothrombin fragment 2 121822-23-9, Hirugen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modified low-**mol.-wt.** heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT 9005-49-6P, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(modified low-**mol.-wt.** heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)
- IT 9000-94-6, Antithrombin 9002-04-4, Blood coagulation factor IIa 9002-05-5, Blood coagulation factor **Xa**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modified low-**mol.-wt.** heparin for inhibition of clot-assocd. coagulation factors and prevention and treatment of thrombotic conditions)

=> d ibib abs hitstr 9

L103 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:528171 HCAPLUS

TITLE: Absolute and comparative subcutaneous bioavailability of ardeparin **sodium**, a low **molecular weight heparin**

AUTHOR(S): Troy, Steven; Fruncillo, Richard; Ozawa, Tsunenori; Mammen, Eberhard; Holloway, Scott; Chiang, Soong

CORPORATE SOURCE: Wyeth-Ayerst Research, Philadelphia, PA, 19101, USA

SOURCE: Thromb. Haemostasis (1997), 78(2), 871-875

CODEN: THHADQ; ISSN: 0340-6245

PUBLISHER: Schattauer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ardeparin **sodium** (Normiflo, Wyeth-Ayerst) is a low mol

. **wt. heparin** undergoing clin. evaluation as an antithrombotic agent. The objective of this study was to evaluate the abs. and comparative bioavailability of ardeparin following s.c. administration of three different formulations [two formulations of ardeparin at 10,000 anti-factor **Xa** (aXa) U/mL, but with different preservatives, and a 20,000 aXa U/mL formulation]. The study was conducted using a randomized 4-period crossover design (three s.c. treatments and one i.v. treatment) in 24 healthy subjects, and the pharmacokinetics of ardeparin were characterized by plasma anti-factor **IIa** (aIIa) and anti-factor **Xa** (aXa) activities. The mean abs. bioavailability of ardeparin based on aIIa activity ranged from 62% to 64% and the mean abs. bioavailability based on aXa activity ranged from 88% to 97%. Based on bioequivalence testing criteria, the three ardeparin formulations were bioequivalent.

=> d ibib abs hitstr 10

L103 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:360010 HCAPLUS

DOCUMENT NUMBER: 122:151072

TITLE: Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, Logiparin). An experimental investigation in healthy volunteers

AUTHOR(S): Holst, J.; Lindblad, B.; Bergqvist, D.; Garre, K.; Nielsen, H.; Hedner, U.; Ostergaard, P. B.

CORPORATE SOURCE: Malmo General Hospital, University Lund, Malmoe, Swed.

SOURCE: Blood Coagulation Fibrinolysis (1994), 5(5), 795-803 ←

CODEN: BLFIE7; ISSN: 0957-5235

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of the present study was to investigate whether tinzaparin sodium (a low-mol.-wt. heparin (LMWH)) was fully and permanently neutralized in vivo in man by protamine sulfate (PS) after i.v. or s.c. injection. Fifty healthy adults equally divided in five age- and sex-matched groups were included. The groups received 50 IU unfractionated heparin (UH)/kg body wt. (b.w.) i.v., 50 anti-factor Xa (**anti-Xa**) IU tinzaparin/kg b.w. i.v., 75 **anti-Xa** IU tinzaparin/kg b.w. s.c., 175 **anti-Xa** IU tinzaparin/kg b.w. s.c., or 1 mL of saline s.c. PS was given as a 10 min infusion in a dose of 1 mg/100 IU of heparin in the four first groups while 0.5 mg PS/kg b.w. was given in the placebo group. In the i.v. groups PS was administered 45 min after the heparin injection, and in the s.c. groups 180 min post-heparin injection. In the UH group PS fully and permanently neutralized all three activities. In the i.v. tinzaparin group PS reversed 80% of the **anti-Xa** activity, while the **anti-IIa** and aPTT activities were fully reversed. A slight, but statistically significant, increase in **anti-Xa** and **anti-IIa** activities were seen following i.v. tinzaparin. In the s.c. groups 60-65% of the obsd. peak **anti-Xa** activity was neutralized, **anti-IIa** was almost completely reversed, and aPTT returned nearly to baseline values. A gradual return of the **anti-Xa** activity (65-75%), **anti-IIa** activity (55%) and aPTT activity (35-45%) was seen in the s.c. groups 3 h after reversal compared with the obsd. peak values. A continuous absorption of tinzaparin from the s.c. depot is presumably the cause of the returned activity. PS caused an 8-27% transient drop in the platelet count in all groups. This study confirms that the **anti-Xa** activity following i.v. and s.c. administration of tinzaparin (a LMWH) is only partially neutralizable by protamine. This is not due to insufficient dosages of the antidote, as an excess of protamine could be demonstrated ex vivo immediately after the protamine infusion. The present results suggest that protamine neutralization of tinzaparin given s.c. should be obtained with intermittent injections or continuous infusion.

=> d ibib abs hitstr 11

L103 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:45510 HCAPLUS

DOCUMENT NUMBER: 120:45510

TITLE: Action and characteristics of parnaparin sodium as an antithrombin III cofactor

AUTHOR(S): Sugiyama, Takayuki; Itoh, Mari; Okitsu, Misako; Natsuga, Tohru; Tomita, Takako

CORPORATE SOURCE: Res. Dep., Shimizu Pharm. Co., Ltd., Shimizu, 424, Japan

SOURCE: Iyakuin Kenkyu (1993), 24(10), 1061-9 ←
CODEN: IYKEDH; ISSN: 0287-0894

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Parnaparin sodium is a low-mol. wt.

heparin coded LHG. The authors investigated the mechanism of action of LHG as an antithrombin III (ATIII) cofactor. From the standpoint of mol. wt., no fractions with mol. wts. below 1500, which were incapable of serving as ATIII cofactor, were detected in LHG or unfractionated heparin (Heparin). However, 79% of LHG consisted of mols. whose mol. wt. was below 5400, which were incapable of expressing any antithrombin activity (**anti-IIa** activity). The mol. wt. of Heparin was mostly in the range above 5400. Using changes in intrinsic fluorescence as an index of binding, the ATIII-binding affinity of LHG was less than that of Heparin, suggesting that LHG includes more fractions with low ATIII binding capacity. Moreover, there was less direct binding of **IIa**, which is an important factor for the expression of **anti-IIa** activity, by LHG than by Heparin. LHG displayed the same degree of enhancing activity on **Xa**-ATIII complex formation, measured by SDS-PAGE and sandwich ELISA, as Heparin with identical **anti-Xa** activity. On the other hand, results were obtained indicating that LHG has weaker enhancing activity on the formation of **IIa**-ATIII complex than Heparin, and that, based on measurement of formation of **Xa**-ATIII and **IIa**-ATIII complexes, LHG has a higher **anti-Xa** activity/**anti-IIa** activity ratio than Heparin.

=> d ibib abs hitstr 12

L103 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:508952 HCAPLUS

DOCUMENT NUMBER: 113:108952

TITLE: Anticoagulant and antithrombotic effects of chemically modified heparins and pentosanpolysulfate

AUTHOR(S): Krupinski, K.; Breddin, H. K.; Casu, B.

CORPORATE SOURCE: Dep. Haematol., Med. Sch., Bialystok, Pol.

SOURCE: Haemostasis (1990), 20(2), 81-92

CODEN: HMTSB7; ISSN: 0301-0147

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pig mucosal **heparin** (GAG 98), in which the binding site for antithrombin had been inactivated by periodate oxidn. (GAG 262), a supersulfated low-**mol.-wt. heparin** (GAG 869), a low-**mol.-wt. heparin** (Fragmin), and **sodium** pentosanpolysulfate have been investigated with regard to their anticoagulant effects in vitro and ex vivo and in an animal thrombosis model in which rat mesenteric venules are damaged by defined laser energy. GAG 262 and pentosanpolysulfate had a markedly reduced anticoagulant effect compared to heparin, Fragmin, and the supersulfated low-**mol.-wt. heparin** fragment. Similarly, the doses necessary to inhibit thrombus formation in the laser model were much higher for GAG 262 and for pentosanpolysulfate compared to heparin and the low-**mol.-wt. heparin** Fragmin, but much lower for the supersulfated heparin fragment. The antithrombotic effect of the low-**mol.-wt. heparin** Fragmin and the supersulfated heparin fragment after s.c. injection lasted much longer than the ex vivo detectable anticoagulant effect. Although some correlation between the antithrombotic and the anticoagulant effect in the laser model is evident, there seems to be no direct correlation between amt. and duration of factor **IIa** or factor **Xa** inhibition and extent and duration of the inhibition of thrombus formation.

=> d ibib abs hitstr 13

L103 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1988:516061 HCAPLUS

DOCUMENT NUMBER: 109:116061

TITLE: Nasal pharmaceuticals containing low-molecular-weight heparin and a fusidate.

INVENTOR(S): Johansen, Kristian Betton

PATENT ASSIGNEE(S): Leo Pharmaceutical Products Ltd., Den.

SOURCE: PCT Int. Appl., 19 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

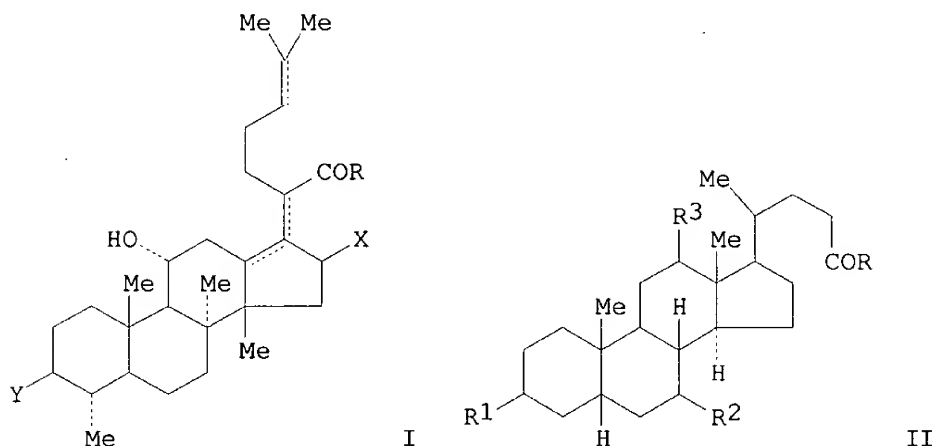
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------------------|------|----------|-----------------|----------|
| WO 8707504 | A1 | 19871217 | WO 1987-DK65 | 19870601 |
| W: DK, JP, US | | | | |
| RW: BE, DE, FR, GB, IT, LU, NL, SE | | | | |
| EP 270639 | A1 | 19880615 | EP 1987-904031 | 19870601 |
| R: BE, DE, FR, GB, IT, LU, NL, SE | | | | |
| JP 63503542 | T2 | 19881222 | JP 1987-503817 | 19870601 |
| DK 8800385 | A | 19880127 | DK 1988-385 | 19880127 |
| PRIORITY APPLN. INFO.: | | | GB 1986-14189 | 19860611 |
| | | | WO 1987-DK65 | 19870601 |

GI



AB Pharmaceuticals contain a nordanthranthrene deriv. (I; R = OH, NHZ; Z = alkyl or aryl optionally substituted by CO₂, SO₃, NH₄⁺; X = H, OH, alkoxy, acyloxy, thioalkyl, thioacyl, halo; Y = OH, alkoxy, acyloxy, halo, alkoxysulfonyl, aryloxysulfonyl; the broken line indicates optional double bond) or a cholane analog (II; R as defined above; R₁-R₃ = H, OH whereby not all R₁-R₃ can be H simultaneously) as a nasal absorption enhancer and low-mol.-wt. heparin (III). Rabbits were administered a soln. contg. 7.5% (wt./vol.) III, 43 mM phosphate buffer, 130 mM NaCl,

15% (wt./vol.) EtOH, and 1% (wt./vol.) Na tauro-24,25-dihydrofusidate into the nasal cavity. The amt. of III administered (i.v.) was 5 mg/kg and its bioavailability was 8.8% of administered dose compared with 2.0% without the absorption enhancer. The antifactor **Xa** activity in a rabbit was 0.03, 0.65, 0.28, 0.43, and 0.24 units/mL after 0, 5, 15, 30, and 60 min, whereas in another, receiving III alone it was 0.03, 0.23, 0, 0.03 units/mL after 0, 5, 15, and 30 min, resp.

=> d ibib abs hitstr 1

L113 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:748867 HCAPLUS

DOCUMENT NUMBER: 130:106770

TITLE: Purification and characterization of a glucuronyltransferase involved in the biosynthesis of the HNK-1 epitope on glycoproteins from rat brain

AUTHOR(S): Terayama, Koji; Seiki, Takashi; Nakamura, Akemi; Matsumori, Kanae; Ohta, Satoru; Oka, Shogo; Sugita, Mutsumi; Kawasaki, Toshisuke

CORPORATE SOURCE: Department of Biological Chemistry and CREST (Core Research for Evolutional Science and Technology) Project, Japan Science and Technology Corporation, Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, 606-8501, Japan

SOURCE: Journal of Biological Chemistry (1998), 273(46), 30295-30300

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The glucuronyltransferase involved in the biosynthesis of the HNK-1 epitope on glycoproteins was purified to an apparent homogeneity from the Nonidet P-40 ext. of 2-wk postnatal rat forebrain by sequential chromatogs. on CM-Sepharose CL-6B, UDP-GlcA-Sepharose 4B, asialo-orosomucoid-Sepharose 4B, Matrex gel Blue A, Mono Q, HiTrap chelating, and HiTrap heparin columns. The purified enzyme migrated as a 45-kDa protein upon SDS-polyacrylamide gel electrophoresis under reducing conditions, but eluted as a 90-kDa protein upon Superose gel filtration in the presence of Nonidet P-40, suggesting that the enzyme forms homodimers under non-denatured conditions. The enzyme transferred **glucuronic** acid to various glycoprotein acceptors bearing **terminal** N-acetyllactosamine structure such as asialo-orosomucoid, asialo-fetuin, and asialo-neural cell adhesion mol., whereas little activity was detected to paragloboside, a precursor glycolipid of the HNK-1 epitope on glycolipids. These results suggested that the enzyme is specifically assocd. with the biosynthesis of the HNK-1 epitope on glycoproteins. Sphingomyelin was specifically required for expression of the enzyme activity. Stearoyl-sphingomyelin (18:0) was the most effective, followed by palmitoyl-sphingomyelin (16:0) and lignoceroyl-sphingomyelin (24:0). Interestingly, activity was demonstrated only for sphingomyelin with a satd. fatty acid, i.e. not for that with an unsatd. fatty acid, regardless of the length of the acyl group.

IT 9005-49-6, Heparin, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(purifn. and characterization of a glucuronyltransferase involved in the biosynthesis of the HNK-1 epitope on glycoproteins from rat brain)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L113 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:698927 HCAPLUS

DOCUMENT NUMBER: 127:345242

TITLE: Serum amyloid P component binds to influenza A virus hemagglutinin and inhibits the virus infection in vitro

AUTHOR(S): Andersen, O.; Ravn, K. Vilsgaard; Sorensen, I. Juul; Jonson, G.; Nielsen, E. Holm; Svebag, S. -E.

CORPORATE SOURCE: Department of Infectious Diseases, Odense University, Odense, DK-5000, Den.

SOURCE: Scandinavian Journal of Immunology (1997), 46(4), 331-337

CODEN: SJIMAX; ISSN: 0300-9475

PUBLISHER: Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Serum amyloid P component (SAP) is a member of the phylogenetically conserved and structurally related group of proteins called pentraxins. SAP exhibits multispecific calcium-dependent binding to oligosaccharides with **terminal** N-acetyl-galactosamine, mannose and **glucuronic** acid. The authors report that SAP can bind to influenza A virus and inhibit agglutination of erythrocytes mediated by the virus subtypes H1N1, H2N2 and H3N2. SAP also inhibits the prodn. of hemagglutinin (HA) and the cytopathogenic effect of influenza A virus in MDCK cells. The binding of SAP to the virus requires physiol. calcium concns. and is blocked by specific SAP antibodies. Denaturated and renaturated SAP retained inhibition of HA. Electron microscopy shows Ca²⁺-dependent binding of SAP to spikes on the viral envelope and immunoblotting indicates that SAP binds to a 50-55 kDa peptide corresponding to the mass of the HA1 peptide. Of several monosaccharides tested only D-mannose interfered with SAP's inhibition of both HA and infectivity. The glycosaminoglycans **heparan** sulfate and **heparin**, which bind SAP, reduced SAPs binding to the virus. The results indicate that the inhibition by SAP is due to steric effects when SAP binds to terminal mannose on oligosaccharides localized close to the sialic acid-binding site of the HA trimer.

IT 9005-49-6, **Heparin**, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(serum amyloid P component binding to influenza A virus hemagglutinin reactivity with)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 3

L113 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1985:574339 HCAPLUS

DOCUMENT NUMBER: 103:174339

TITLE: Distribution of glucuronic and iduronic acid units in
heparin chains

AUTHOR(S): Radoff, Steven; Danishefsky, Isidore

CORPORATE SOURCE: Dep. Biochem., New York Med. Coll., Valhalla, NY,
10595, USA

SOURCE: J. Biol. Chem. (1985), 260(28), 15106-11 ←

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The distribution of glucuronic and iduronic acid within the chains of anticoagulant-active and -inactive beef lung **heparin** was investigated. A fraction with an av. **mol. wt.** of 19,500 was isolated from the heterodisperse mixt. and then sepd. into active and inactive components by affinity chromatog. Each sample was linked through its reducing terminus to tyramine, reduced with NaB₃H₄, and bound covalently to Sepharose via an azo bridge. The bound, reduced **heparin** was treated with a limited amt. of HNO₂ and the degraded fragments were removed. The sections of the chain contiguous with the original reducing terminus were then detached from the insol. matrix by reaction with Na dithionite. The recovered polysaccharide was fractionated according to size on Sephadex G-200 and the amt. of each uronic acid in the individual fractions was detd. Inactive **heparin** showed a const. percentage of glucuronic acid in all fragments, i.e., .apprx.8.9% of the total uronic acid. With active **heparin**, the percentage of **glucuronic** acid increased with the distance from the reducing **terminus** of the polysaccharide chain, ranging 9.5-20% of the uronic acids. Thus, the biosynthesis of active **heparin** apparently involves unique reactions or specific processing of the macromol.

IT 9005-49-6, biological studies

RL: BIOL (Biological study)

(glucuronate and iduronate distribution in, of lung, anticoagulant activity in relation to)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 4

L113 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1985:451764 HCAPLUS

DOCUMENT NUMBER: 103:51764

TITLE: Oligosaccharides generated by an endoglucuronidase are intermediates in the intracellular degradation of **heparan** sulfate proteoglycans

AUTHOR(S): Kjellen, Lena; Pertoft, Haakan; Oldberg, Aake; Hoeoek, Magnus

CORPORATE SOURCE: Biomed. Cent., Univ. Uppsala, Uppsala, Swed.

SOURCE: J. Biol. Chem. (1985), 260(14), 8416-22

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An intracellular **heparan** sulfate oligosaccharide was identified in rat hepatocytes cultured in the presence of [35S]sulfate. Pulse-chase expts. suggested that [35S]sulfate is first incorporated into **heparan** sulfate proteoglycans which are subsequently converted to the low-mol.-wt. component. The oligosaccharide (mol. wt. 7000) contained little or no protein and was also present in rat liver homogenates. Subcellular fractionation and d.-gradient centrifugation in Percoll of liver homogenates demonstrated that the oligosaccharide was present in lysosomes or in particles of similar distribution and buoyant d. Structural anal. of oligosaccharides isolated from a rat liver lysosomal fraction indicated that **glucuronic** acid is present in the reducing end of the oligosaccharide and that this residue is preferentially linked to an N-acetylated glucosamine unit. Apparently, the **heparan** sulfate oligosaccharide is generated through the action of a **heparan** sulfate-degrading endoglucuronidase previously found in human platelets and rat liver (Oldberg, A.; et al., 1980).

=> d ibib abs hitstr 5

L113 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1982:540766 HCAPLUS

DOCUMENT NUMBER: 97:140766

TITLE: Purification and properties of human platelet
heparitinaseAUTHOR(S): Oosta, Gary M.; Favreau, Leonard V.; Beeler, David L.;
Rosenberg, Robert D.CORPORATE SOURCE: Harvard Med. Sch., Beth Israel Hosp., Boston, MA,
02115, USA

SOURCE: J. Biol. Chem. (1982), 257(19), 11249-55

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Heparitinase (I), an endoglycosidase which cleaves **heparin** and **heparan** sulfate, was isolated from outdated human blood platelets by freeze-thaw solubilization, **heparin**-Sephadex chromatog., DEAE-cellulose chromatog., hydroxylapatite chromatog., octyl-agarose chromatog., con A-Sephadex chromatog., and Sephacryl S-200 gel filtration. The overall extent of purifn. of platelet I was .apprx.240,000-fold and the overall yield was .apprx.5.6% as compared to the initial freeze-thaw solubilization prepn. The final product was phys. homogeneous as judged by disc gel electrophoresis at acidic pH as well as by gel filtration chromatog. and exhibited an apparent **mol. wt.** of .apprx.134,000. I was apparently present within platelet lysosomes. The biol. potency of I was examd. as a function of pH. I was max. active at pH 5.5-7.5. However, I possessed minimal ability to cleave **heparin** at pH <4.0 or >9.0. The substrate specificity of I was detd. by identifying susceptible linkages within the **heparin** **mol.** that could be cleaved by the above component. Apparently, I was only able to hydrolyze glucuronosyl-glucosamine linkages. Investigation of the structure of the disaccharide which lies on the nonreducing **end** of the cleaved **glucuronic** acid residue suggested that N-sulfation of the glucosamine moiety or ester sulfation of the adjacent iduronic acid groups were not essential for bond scission.

IT 9005-49-6, biological studies

RL: RCT (Reactant)

(cleavage of, by heparitinase of human blood platelets, pH effect on)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 6

L113 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1982:110167 HCAPLUS
 DOCUMENT NUMBER: 96:110167
 TITLE: Improved anticoagulant substance
 INVENTOR(S): Barnett, William E.
 PATENT ASSIGNEE(S): Riker Laboratories, Inc., USA
 SOURCE: PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------------------|------|----------|-----------------|----------|
| WO 8103276 | A1 | 19811126 | WO 1981-US519 | 19810417 |
| W: AU, DK, JP, NO | | | | |
| RW: AT, CH, DE, FR, GB, LU, NL, SE | | | | |
| US 4351938 | A | 19820928 | US 1980-151163 | 19800519 |
| AU 8171716 | A1 | 19811207 | AU 1981-71716 | 19810417 |
| JP 57500612 | T2 | 19820408 | JP 1981-501646 | 19810417 |
| EP 53612 | A1 | 19820616 | EP 1981-901249 | 19810417 |
| R: AT, CH, DE, FR, GB, LU, NL, SE | | | | |
| ZA 8103321 | A | 19820526 | ZA 1981-3321 | 19810518 |
| BE 888864 | A1 | 19811119 | BE 1981-204833 | 19810519 |
| DK 8200189 | A | 19820118 | DK 1982-189 | 19820118 |
| NO 8200136 | A | 19820118 | NO 1982-136 | 19820118 |
| US 4438261 | A | 19840320 | US 1982-384032 | 19820601 |
| PRIORITY APPLN. INFO.: | | | US 1980-151163 | 19800519 |
| | | | WO 1981-US519 | 19810417 |

AB A partially depolymd. **heparin** product, which has an av. **mol. wt.** of 2000-7000 daltons, is obtained by treating a com. **heparin** salt with HNO₂ under controlled conditions. This product can be used for inhibiting blood coagulation. Thus, 20 g com. Na **heparin** [9041-08-1] was dissolved in 1 L aq. AcOH (1% by vol.) and treated with 160 mL 0.4% NaNO₂ soln. and the mixt. stirred at 20.degree. for 3.5 h. The soln. was then frozen, and lyophilized to yield 19.8 g granular white solid. The **mol. wt.**, as detd. by high-performance liq. chromatog. with 1.5M NaCl as the mobile phase, is 2400-6100 Daltons, the polydispersity is 1.9 and wt.% of the sample having **mol. wt.** >15,000 D is 4.2. The USP potency is 41.0 units/mg. The **end** group anal. showed the presence of anhydromannose, iduronic acid and **glucuronic** acid at concns. 98, 39.6, and 19.5 nMol/mg, resp.

=> d ibib abs hitstr 7

L113 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1981:492922 HCAPLUS

DOCUMENT NUMBER: 95:92922

TITLE: Biosynthesis of **heparin**. Transfer of N-acetylglucosamine to **heparan** sulfate oligosaccharides

AUTHOR(S): Forsee, W. Thomas; Roden, Lennart

CORPORATE SOURCE: Inst. Dent. Res., Univ. Alabama, Birmingham, AL, 35294, USA

SOURCE: J. Biol. Chem. (1981), 256(14), 7240-7

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The N-acetylglucosaminyltransferase which acts in conjunction with a glucuronosyltransferase in the biosynthesis of the polysaccharide backbone of **heparin** was investigated. Substrates for the enzyme were prepd. from a low-sulfated, glucuronic acid-rich **heparan** sulfate fraction, which was desulfated and subsequently treated with HNO₂; the products of the deaminative cleavage were fractionated by gel chromatog. on Sephadex G-25, yielding a series of oligosaccharides which ranged from di- to dodecasaccharides. Characterization of the tetra-, hexa-, and octasaccharide fractions by digestion with .beta.-glucuronidase showed that close to 60% of the nonreducing **termini** in each fraction was occupied by **glucuronic** acid. When incubated with a solubilized enzyme prepn. from a mouse mastocytoma which has been partially purified by chromatog. on DEAE-cellulose, all oligosaccharide fractions except the disaccharides served as acceptors for N-acetylglucosaminyl transfer. Anal. of the products showed that transfer of a single N-acetylglucosamine residue had occurred and that the newly formed glycosidic linkage was of the .alpha. configuration. Acceptor activity was abolished by digestion with .beta.-glucuronidase, indicating that glucuronic acid units, but not iduronic acid residues, could serve as substrates. The enzyme exhibited decreasing Km values of 8.7, 1.3, and 0.07 mM for the tetra-, hexa-, and octasaccharides, resp., suggesting that the affinity of the transferase for the growing polysaccharide may increase markedly in the early stages of polymn. When the octasaccharide fraction was incubated with a particulate microsomal enzyme prepn. in the presence of both UDP-N-acetylglucosamine and UDP-glucuronic acid, it served as a primer for the formation of a high-mol.-wt . product.

IT 9005-49-6, biological studies

RL: FORM (Formation, nonpreparative)

(formation of, substrates for acetylglucoaminyltransferase in)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 8

L113 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1980:53939 HCAPLUS

DOCUMENT NUMBER: 92:53939

TITLE: Substrate specificity of a **heparan**
sulfate-degrading endoglucuronidase from human
placenta

AUTHOR(S): Klein, Udo; Von Figura, Kurt

CORPORATE SOURCE: Physiol.-Chem. Inst., Univ. Muenster, Muenster,
D-4400, Fed. Rep. Ger.

SOURCE: Hoppe-Seyler's Z. Physiol. Chem. (1979), 360(10),
1465-71

CODEN: HSZPAZ; ISSN: 0018-4888

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A **heparan** sulfate-degrading endoglucuronidase was isolated from human placenta and partially purified by affinity chromatog. of **heparin** sulfate-Sepharose 4B. The endoglucuronidase had a mol. wt. of .apprx.100,000 estd. by gel chromatog. and a broad pH optimum between pH 4 and pH 6. Carboxyl-reduced **heparan** sulfate was not split by partially purified endoglucuronidase, but inhibited the action of that enzyme towards nonmodified **heparan** sulfate. Low-mol.-wt.- **heparan** sulfate (mol. wt. .apprxeq.3000) was not attacked by the endoglucuronidase. N-Desulfated **heparan** sulfate and **heparin** were only weak substrates. The amino sugar adjacent to the **glucuronic** acid residue appearing at the reducing **terminal** of **heparan** sulfate fragments liberated by the endoglucuronidase appears to be exclusively N-acetylated glucosamine.

IT 9005-49-6, biological studies

RL: PRP (Properties)

(degrdn. of, by endoglucuronidase of placenta)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 9

L113 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1979:179925 HCAPLUS

DOCUMENT NUMBER: 90:179925

TITLE: Correlation between structure and function of
heparin

AUTHOR(S): Rosenberg, Robert D.; Lam, Lun

CORPORATE SOURCE: Sidney Farber Cancer Inst., Beth Israel Hosp., Boston,
Mass., USASOURCE: Proc. Natl. Acad. Sci. U. S. A. (1979), 76(3), 1218-22
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Crude porcine **heparin** [9005-49-6] was fractionated to obtain highly active as well as relatively inactive species of mol . wt. .apprxeq.7000 with specific anticoagulant activities of 360 and 12 units/mg, resp. Nitrous acid degrdn. of both of these polymers yielded a tetrasaccharide fraction, I.beta., that contained equimolar amts. of iduronic and **glucuronic** acids, possessed an internal N-acetylated glucosamine, and carried anhydromannitol at the reducing end position. The I.beta. tetrasaccharide derived from the highly active **heparin**, I.beta.a, was recovered in a yield of 1.1 mol/7000 daltons. At least 95% of the I.beta.a was a single structure that consisted of the following unique monosaccharide sequence: L-iduronic acid .fwdarw. N-acetyl-D-glucosamine-6-sulfate .fwdarw. D-glucuronic acid .fwdarw. D-glucosamine-N,6-disulfate. The I.beta. tetrasaccharide fraction from relatively inactive mucopolysaccharide, I.beta.i, was recovered in a yield of 0.3 mol/7000 daltons and was a mixt. of several components. Only 8.5% of the I.beta.i tetrasaccharide fraction exhibited the same uronic acid placement and sulfate group position found in I.beta.a. Thus, 2.6% of relatively inactive mucopolysaccharide mols. contain the unique tetrasaccharide sequence found within each mol. of highly active **heparin**. Given the correlation between abundance of this unique I.beta.a tetrasaccharide sequence and biol. potency, this structure represents the crit. site responsible for anticoagulant activity.

IT 9005-49-6, biological studies

RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)

(anticoagulant activity of, mol. structure in relation to)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 10

L113 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1978:540209 HCAPLUS

DOCUMENT NUMBER: 89:140209

TITLE: Structure-function relationships of **heparin** species

AUTHOR(S): Rosenberg, Robert D.; Armand, Gerard; Lam, Lun

CORPORATE SOURCE: Sidney Farber Cancer Inst., Beth Israel Hosp., Boston, Mass., USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1978), 75(7), 3065-9
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Porcine **heparin** species of low mol. wt., with an av. specific anticoagulant activity of 96 units/mg were fractionated by affinity chromatog. Highly active and relatively inactive prepn. of similar size were obtained with specific anticoagulant activities of 360 and 4 units/mg, resp. The highly active **heparin** fraction possessed 1.1 addnl. residues of glucuronic acid [6556-12-3] and 1.5 fewer residues of N-sulfated glucosamine per mol. compared to the relatively inactive species. This decrease in N-sulfated glucosamine appeared to be secondary to a corresponding increase in N-acetylated glucosamine. This form also contained a tetrasaccharide sequence with a N-sulfated glucosamine at its reducing **end** as well as equiv. amts. of **glucuronic** acid and iduronic acid [3402-98-0]. The internal glucosamine residue of this sequence appeared to be N-acetylated. Sufficient amts. of this tetrasaccharide sequence were present within the highly active prepn. such that each mol. may be endowed with this structure. The relatively inactive product contained a decreased quantity of this tetrasaccharide sequence such that only .simeq.20% of these mols. may possess this structure. The mean distance between nonsulfated uronic acid residues of the highly active species was smaller than that sepg. similar residues of the relatively inactive product. In addn., a larger no. of the nonsulfated uronic acid residues of the highly active material appeared either to be present in a restricted region of the mol. sepd. only by glucosamine residues or to be located at pentultimate positions within the polysaccharide chain.

IT 9005-49-6, biological studies

RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)

(anticoagulant activity of fractions of)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 11

L113 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1975:166426 HCAPLUS

DOCUMENT NUMBER: 82:166426

TITLE: Cleavage of macromolecular **heparin** by an enzyme from mouse mastocytoma

AUTHOR(S): Ogren, Soren; Lindahl, Ulf

CORPORATE SOURCE: Inst. Med. Chem., Univ. Uppsala, Uppsala, Swed.

SOURCE: J. Biol. Chem. (1975), 250(7), 2690-7

CODEN: JBCHA3

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Heparinase**, isolated from a transplantable mouse mastocytoma, degraded macromol., ³⁵S-labeled, mastocytomal **heparin** (Kav .apprx.0.25) to products similar in size to com. **heparin** (Kav .apprx.0.85), apparently by nonrandom cleavage of a limited no. of glycosidic linkages/mol. Prolonged incubation times did not result in further product degrdn. No significant depolymerizing activity was obsd. with any other glycosaminoglycan tested. The pH optimum for degrdn. of macromol. **heparin** was .apprx. pH 5. The nature of the linkage cleaved by the **heparinase** was investigated by redn. of nonlabeled polysaccharide degrdn. products with Na borohydride. The degraded chains (but not the macromol substrate) incorporated significant amts. of tritium. An essentially monodisperse fraction of the labeled, degraded **heparin** had a mol. wt. of 14,500. By relating the mol. wt. to the specific activity of the prepn., the amt. of reducible groups was calcd. as .apprx.1/mol. The ³H-labeled **heparin** was degraded to monosaccharides by a combination of acid hydrolysis and cleavage due to deamination with nitrous acid. Anal. of the degrdn. products showed a major radioactive component which behaved like L-gulonic acid. Since tritiated gulonic acid would be the expected redn. product of a polysaccharide mol. contg. a **glucuronic** acid residue in **terminal** position, these results tentatively suggest that **heparinase** is an endoglucuronidase. By direct deaminative cleavage of the ³H-labeled **heparin**, the glucosamine unit in the penultimate position was 52% N-sulfated and 48% N-acetylated. As only 14% of the glucosamine was N-acetylated in the macromol. **heparin** substrate the cleavage of this polysaccharide by the **heparinase** apparently occurs in regions more abundant in N-acetylated glucosamine residues than other portions of the mol. The possibility that formation and degrdn. of macromol. **heparin** occurs in mammalian species other than rodents is discussed.

=> d ibib abs hitstr 12

L113 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1966:466666 HCAPLUS

DOCUMENT NUMBER: 65:66666

ORIGINAL REFERENCE NO.: 65:12451b-f

TITLE: The carbohydrate-protein linkage in the protein complex of acid mucopolysaccharides

AUTHOR(S): Roden, Lennart

CORPORATE SOURCE: Univ. of Chicago

SOURCE: Struct. Function Connective Skeletal Tissue, Proc., St. Andrews, Scot. (1965), Volume Date 1964 141-5

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two crude glycopeptide fractions were sepd. by gel filtration on Sephadex G-50. The fraction with **mol. wt.** .apprx.1800 contained approx. 40% of its hexosamine as glucosamine, indicating the presence of a relatively large portion of keratosulfate. The lesser fraction, **mol. wt.** .apprx.1100, contg. little glucosamine had a molar ratio of uronic acid to hexosamine of 2:1. This fraction contained galactose and xylose. The molar ratio of uronic acid to galactose to xylose was approx. 2:2:1. Xylose was probably involved in the carbohydrate-protein linkage. The glycopeptides contained a **terminal** trisaccharide unit, **glucuronic acid-galactosamineglucuronic acid-**, from the chondroitin 4-sulfate chains. A disaccharide, composed of glucuronic acid and galactose linked by a .beta.-glucuronidic linkage, was isolated, upon hydrolysis, from chondroitin 4-sulfate glycopeptides. The galactose moiety was at the reducing end of this substance; the linkage was either 1 .fwdarw. 3 or 1 .fwdarw. 4. Thus a glucuronosyl galactose residue was a structural unit in the carbohydrate-protein linkage region. The analyses of the products obtained by mild acid hydrolysis of chondroitin 4-sulfate glycopeptides and by periodate oxidn. of xylosylserine indicated that xylose was linked by a glycosidic linkage to the OH group of serine. In peptide-contg. **heparin** prepns. serine was the major amino acid and in certain prepns. it was the only amino acid present in significant amts. Galactose and xylose were also present in such **heparin** samples. Mild acid hydrolysis of **heparin** contg. serine as the major amino acid produced 2 carbohydrate-serine compds., identical in compn. and properties with the serine-contg. compds. obtained from chondroitin 4-sulfate glycopeptides. **Heparin** in the native state was linked to protein in a manner similar to that of chondroitin 4-sulfate. A trisaccharide, galactosylgalactosylxylose, was isolated from **heparin**. The quant. analyses of the chondroitin 4-sulfate glycopeptides also indicated that 2 galactose mols. might be involved in the linkage area. The following general arrangement was suggested for the complexes studied: uronic acid-hexosamine-glucuronic acidgalactose-galactose-xylose-serine.

=> d ibib abs hitstr

L112 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:103246 HCAPLUS

DOCUMENT NUMBER: 116:103246

TITLE: Proton NMR spectroscopic studies on the interactions between human plasma antithrombin III and defined low molecular weight heparin fragments

AUTHOR(S): Horne, Angela; Gettins, Peter

CORPORATE SOURCE: Sch. Med., Vanderbilt Univ., Nashville, TN, 37232-0146, USA

SOURCE: Biochemistry (1992), 31(8), 2286-94

CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of length and compn. upon the antithrombin-binding properties of **heparin** were investigated for 2 series of structurally related **heparin** oligosaccharides. Each series consisted of a tetrasaccharide, hexasaccharide, and octasaccharide **heparin** fragment composed of alternating hexuronic acid (either iduronate 2-sulfate or glucuronate) and glucosamine 6,N-disulfate residues. These 2 series represented dominant structural motifs in intact **heparin** and differed from each other by the presence of a **glucuronic** acid in one series in place of an iduronate 2-sulfate residue penultimate to the reducing end of the fragment. Perturbations to the 1H resonances in the NMR spectrum of antithrombin upon binding of the 2 series of **heparin** fragments were compared to those generated by intact **heparin** binding, as well as to the effects of binding of a synthetic high-affinity pentasaccharide. All of the **heparin** fragments examd. appeared to bind to antithrombin at the same site. Three of the **heparin** fragments produced almost identical perturbations in the antithrombin 1H NMR spectrum compared to binding of intact **heparin**, including perturbations of resonances from Trp-49. This indicated that neither the glucuronic acid nor the trisulfated glucosamine residue (structural elements known to be part of the high-affinity **heparin** motif) are necessary for the majority of the conformational changes induced upon **heparin** fragment binding to antithrombin. However, the low anticoagulant activity of these fragments indicated that the changes in protein conformation upon fragment binding, as manifested by these 1H resonance perturbations, are not sufficient for catalytic activation of the inhibitor. Since there were few differences between the difference spectra generated by active **heparin** (either pentasaccharide or the intact species) as compared to the inactive **heparin** fragments, further limited conformational changes that arise from the presence of elements of the high-affinity motif that are absent in the **heparin** fragments considered here must be necessary for inhibitor activation by **heparin**.

IT 9005-49-6, **Heparin**, biological studies

RL: BIOL (Biological study)

(antithrombin III of human interaction with, protein conformation and activity in relation to)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ind

L112 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS
 CC 13-5 (Mammalian Biochemistry)
 Section cross-reference(s): 1
 ST antithrombin interaction **heparin** fragment NMR
 IT Molecular structure-biological activity relationship
 (antithrombin-activating, of **heparin** low-mol.-
 wt. fragments)
 IT Conformation and Conformers
 (of antithrombin III, of human, low-mol.-wt.
heparin fragments effect on)
 IT Kinetics, enzymic
 (of inhibition, of blood-coagulation factor **Xa** by human
 antithrombin III, low-mol.-wt. **heparin**
 fragments effect on)
 IT 9005-49-6, **Heparin**, biological studies
 RL: BIOL (Biological study)
 (antithrombin III of human interaction with, protein conformation and
 activity in relation to)
 IT 89847-99-4 89872-05-9 121596-31-4 138459-88-8 138459-89-9
 138459-90-2
 RL: BIOL (Biological study)
 (antithrombin III of human interaction with, protein conformation and
 activity response to, oligosaccharide structure in relation to)
 IT 9000-94-6, Antithrombin
 RL: BIOL (Biological study)
 (**heparin** low-mol.-wt. fragments
 interaction with, of human, protein conformation and activity in
 relation to)
 IT 9002-05-5, Blood-coagulation factor **Xa**
 RL: BIOL (Biological study)
 (inhibition of, by antithrombin III of human, kinetics of, low-
 mol.-wt. **heparin** fragments effect on)

=> d ibib abs hitstr 1

L56 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2001:137173 HCAPLUS
 DOCUMENT NUMBER: 134:178396
 TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
 INVENTOR(S): Del Soldato, Piero
 PATENT ASSIGNEE(S): Nicox S.A., Fr.
 SOURCE: PCT Int. Appl., 94 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2001012584 | A2 | 20010222 | WO 2000-EP7225 | 20000727 |
| W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG BR 2000013264 A 20020416 BR 2000-13264 20000727 PRIORITY APPLN. INFO.: IT 1999-MI1817 A 19990812 WO 2000-EP7225 W 20000727 | | | | |

OTHER SOURCE(S): MARPAT 134:178396

AB Compds. or their salts of general formula (I): A-B-N(O)s wherein: s is an integer equal to 1 or 2; A = R-T1-, wherein R is the drug radical and T1 = (CO)t or (X)t', wherein X = O, S, NR1c, R1c is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -TB -X2-O- wherein TB = (CO) when t = 0, TB = X when t' = 0, X being as above defined; X2, bivalent radical, is such that the precursor drug of A and the precursor of B meet resp. the pharmacol. tests described in the description. Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT 9005-49-6, Dalteparin, reactions

RL: RCT (Reactant); RACT (Reactant or reagent)

(antithrombotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Connective Tissue Research 1975, vol. 3.
 73-79.

=> d ibib abs hitstr 2

L56 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:742057 HCAPLUS

DOCUMENT NUMBER: 133:309791

TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction

INVENTOR(S): Del Soldato, Piero

PATENT ASSIGNEE(S): Nicox S.A., Fr.

SOURCE: PCT Int. Appl., 140 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2000061541 | A2 | 20001019 | WO 2000-EP3239 | 20000411 |
| WO 2000061541 | A3 | 20010927 | | |
| W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| IT 1311923 | B1 | 20020320 | IT 1999-MI752 | 19990413 |
| BR 2000009703 | A | 20020108 | BR 2000-9703 | 20000411 |
| EP 1169298 | A2 | 20020109 | EP 2000-926870 | 20000411 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| NO 2001004928 | A | 20011213 | NO 2001-4928 | 20011010 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | IT 1999-MI752 | A 19990413 |
| | | | WO 2000-EP3239 | W 20000411 |

OTHER SOURCE(S): MARPAT 133:309791

AB Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT 9005-49-6, Dalteparin, reactions

RL: RCT (Reactant); RACT (Reactant or reagent)

(antithrombotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d kwic 2

L56 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2002 ACS

IT 50-59-9, Cephaloridine 54-85-3, Isoniazid 56-75-7, Chloramphenicol 57-62-5 57-67-0, Sulfaguanidine 57-68-1, Sulfamethazine 57-92-1, Streptomycin, reactions 60-54-8, Tetracycline 61-24-5, Cephalosporin C 61-33-6, Benzyl penicillinic acid, reactions 61-72-3,

Cloxacillin 63-74-1, Sulfanilamide 65-49-6, p-Aminosalicylic acid 66-79-5, Oxacillin 68-35-9, Sulfadiazine 68-41-7, Cycloserine 72-14-0, Sulfathiazole 74-55-5, Ethambutol 74-79-3, Arginine, reactions 79-57-2, Oxytetracycline 80-02-4, 2-p-Sulfanilylanilinoethanol 80-03-5, Acediasulfone 80-08-0, Dapsone 80-32-0, Sulfachlorpyridazine 80-35-3, Sulfamethoxypyridazine 87-08-1, Penicillin V 87-09-2, Penicillin O 94-19-9, Sulfaethidole 103-12-8, Sulfamidochrysoidine 113-98-4, Penicillin G potassium 114-07-8, Erythromycin 115-68-4, Sulfadiazine 116-42-7, Sulfaproxyline 116-44-9, Sulfapyrazine 119-59-5, 4,4'-Sulfinyldianiline 120-34-3, N-Sulfanilyl-3,4-xylamide 122-11-2, Sulfadimethoxine 127-33-3, Demeclocycline 127-69-5, Sulfisoxazole 127-71-9, Sulfabenzamide 127-79-7, Sulfamerazine 128-46-1, Dihydrostreptomycin 130-16-5, Cloxyquin 132-92-3, Methicillin sodium 132-93-4, Phenethicillin potassium 133-11-9, Phenyl aminosalicylate 138-39-6, Mafenide 144-80-9, Sulfacetamide 144-82-1, Sulfamethizole 144-83-2, Sulfapyridine 152-47-6, Sulfalene 153-61-7, Cephalothin 154-21-2, Lincomycin 303-81-1, Novobiocin 389-08-2 443-48-1, Metronidazole 473-30-3, Thiazolsulfone 485-41-6, Sulfachrysoidine 495-84-1, Salinazid 515-49-1, Sulfathiourea 515-59-3, Sulfamethylthiazole 515-64-0, Sulfisomidine 525-94-0, Penicillin N 526-08-9, Sulfaphenazole 547-44-4, Sulfanilylurea 547-52-4, N4-Sulfanilylsulfanilamide 547-53-5, 4'-(Methylsulfamoyl)sulfanilamide 551-27-9, Propicillin 599-88-2, Sulfaperine 651-06-9, Sulfameter 723-46-6, Sulfamethoxazole 729-99-7, Sulfamoxole 751-97-3, Rolitetracycline 808-26-4, Sancycline 914-00-1, Methacycline 992-21-2, Lymecycline 1110-80-1, Pipacycline 1181-54-0, Clomocycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 1596-63-0, Quinacillin 1614-20-6, Nifurprazine 1695-77-8, Spectinomycin 1926-49-4, Clometocillin 1984-94-7, Sulfasymazine 2013-58-3, Meclocycline 2030-63-9, Clofazimine 2315-08-4, Salazosulfadimidine 2447-57-6, Sulfadoxine 2750-76-7, Rifamide 2751-09-9, Troleandomycin 2779-55-7, Opiniazone 3116-76-5, Dicloxacillin 3485-14-1, Cyclacillin 3511-16-8, Hetacillin 3577-01-3, Cephaloglycin 3590-05-4, Acetyl sulfamethoxypyrazine 3691-74-5, Glyconiazide 3772-76-7, Sulfamethomidine 3922-90-5, Oleandomycin 4008-48-4, Nitroxoline 4393-19-5, p-Sulfanilylbenzyl amine 4564-87-8, Carbomycin 4697-36-3, Carbenicillin 5250-39-5, Floxacillin 5934-14-5, Succisulfone 6202-21-7, 4-Sulfanilamidosalicylic acid 6489-97-0, Metampicillin 6946-29-8, p-Aminosalicylic acid hydrazide 6998-60-3, Rifamycin 7542-37-2, Paromomycin 8025-81-8, Spiramycin 10118-90-8, Minocycline 11003-38-6, Capreomycin 11006-76-1, Virginiamycin 12650-69-0, Mupirocin 13411-16-0, Nifurpirinol 13838-08-9, Azidamfenicol 13898-58-3, Benzoylpas 13925-12-7, Myxin 15599-51-6, Apicycline 15686-71-2, Cephalixin 16545-11-2, Guamecycline 16846-24-5, Josamycin 17243-38-8, Azidocillin 17784-12-2, Sulfacytine 18323-44-9, Clindamycin 19562-30-2, Piromidic acid 23239-41-0, Cephaetrile sodium 23477-98-7, Sedecamycin 24356-60-3, Cephapirin sodium 25546-65-0, Ribostamycin 25953-19-9, Cefazolin 26086-49-7, Deoxydihydrostreptomycin 26774-90-3, Epicillin 26787-78-0, Amoxicillin 26973-24-0, Ceftezole 27031-08-9, Sulfaguanole 28657-80-9, Cinoxacin 32385-11-8, Sisomicin 32887-01-7, Amdinocillin 32909-92-5, Sulfametrole 32986-56-4, Tobramycin 32988-50-4, Viomycin 33103-22-9, Enviomycin 33404-78-3, Negamycin 33817-20-8, Pivampicillin 34444-01-4, Cefamandole 34493-98-6, Dibekacin 34787-01-4, Ticarcillin 35457-80-8, Midecamycin 35531-88-5, Carindacillin 35607-66-0, Cefoxitin 35834-26-5, Rosaramicin 37091-66-0, Azlocillin 37321-09-8, Apramycin 37517-28-5, Amikacin 38129-37-2, Bicozamycin 38821-53-3, Cephradine 41744-40-5, Sulbenicillin 42835-25-6, Flumequine 47747-56-8, Talampicillin 50370-12-2, Cefadroxil 50972-17-3,

Bacampicillin 51025-85-5, Arbekacin 51481-65-3, Mezlocillin 51627-14-6, Cefatrizine 51762-05-1, Cefroxadine 51940-44-4, Pipemidic acid 52093-21-7, Micronomicin 52152-93-9 53994-73-3, Cefaclor 55268-75-2, Cefuroxime 55881-07-7, Miokamycin 56187-47-4, Cefazedone 56391-56-1, Netilmicin 56796-20-4, Cefmetazole 58001-44-8, Clavulanic acid 60925-61-3, Ceforanide 61270-58-4, Cefonicid 61379-65-5, Rifapentine 61477-96-1, Piperacillin 61622-34-2, Cefotiam 62013-04-1, Dirythromycin 62893-19-0, Cefoperazone 63358-49-6, Aspoxicillin 63469-19-2, Apalcillin 63527-52-6, Cefotaxime 63836-75-9, Cephalixin pivaloxymethyl ester 64221-86-9, Imipenem 64952-97-2, Moxalactam 65052-63-3, Cefetamet 65085-01-0, Cefmenoxime 66148-78-5, Temocillin 68373-14-8, Sulbactam 68401-81-0, Ceftizoxime 69712-56-7, Cefotetan 69739-16-8, Cefodizime 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 70797-11-4, Cefpiramide 71426-83-0, Fortimicin 72558-82-8, Ceftazidime 72559-06-9, Rifabutine 73384-59-5 74011-58-8, Enoxacin 74014-51-0, Rokitamycin 76470-66-1, Loracarbef 76497-13-7, Sultamicillin 76610-84-9, Cefbuperazone 78110-38-0, Aztreonam 79350-37-1, Cefixime 79548-73-5, Pirlimycin 79660-72-3, Fleroxacin 80370-57-6, Ceftiofur 80621-81-4, Rifaximin 81103-11-9, Clarithromycin 82219-78-1, Cefuzonam 82419-36-1, Ofloxacin 82547-58-8, Cefteram 83905-01-5, Azithromycin 84305-41-9, Cefminox 84845-57-8, Ritipenem 84880-03-5, Cefpimizole 84957-29-9, Cefpirome 85721-33-1, Ciprofloxacin 86273-18-9, Lenampicillin 87239-81-4, Cefpodoxime proxetil 87638-04-8, Carumonam 87726-17-8, Panipenem 88040-23-7, Cefepime 88669-04-9, Trospectomycin 91832-40-5, Cefdinir 92665-29-7, Cefprozil 93106-60-6, Enrofloxacin 96036-03-2, Meropenem 97519-39-6, Ceftibuten 98079-51-7 98106-17-3, Difloxacin

RL: RCT (Reactant); RACT (Reactant or reagent)

(antibiotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

IT 58-32-2, Dipyridamole 68-90-6, Benziodarone 100-55-0, Nicotinyl alcohol 322-79-2, Triflusal 390-64-7, Prenylamine 395-28-8, Isoxsuprine 437-74-1, Xanthinol niacinate 447-41-6, Nyldrin 456-59-7, Cyclandelate 574-77-6, Papaveroline 987-78-0, Citicoline 3611-72-1, Clobenfurool 3703-79-5, Bamethan 5638-76-6, Betahistine 6621-47-2, Perhexiline 9005-49-6, Dalteparin, reactions 13042-18-7, Fendiline 14838-15-4, Phenylpropanolamine 22103-14-6, Bufeniode 23210-56-2, Ifenprodil 36702-83-7, Tinofedrine 37270-89-6, Nadroparin calcium 42794-76-3, Midodrine 54767-75-8, Suloctidil 57475-17-9, Brovincamine 57653-27-7, Droprenilamine 63610-08-2, Indobufen 74863-84-6, Argatroban 78919-13-8, Iloprost 81110-73-8, Acetorphan 82571-53-7, Ozagrel 89667-40-3 110140-89-1, Ridogrel 144412-49-7, Lamifiban

RL: RCT (Reactant); RACT (Reactant or reagent)

(antithrombotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

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L56 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:742053 HCAPLUS
 DOCUMENT NUMBER: 133:310142
 TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
 INVENTOR(S): Del Soldato, Piero
 PATENT ASSIGNEE(S): Nicox S.A., Fr.
 SOURCE: PCT Int. Appl., 159 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2000061537 | A2 | 20001019 | WO 2000-EP3234 | 20000411 |
| WO 2000061537 | A3 | 20010927 | | |
| W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| IT 1311924 | B1 | 20020320 | IT 1999-MI753 | 19990413 |
| BR 2000009702 | A | 20020108 | BR 2000-9702 | 20000411 |
| EP 1169294 | A2 | 20020109 | EP 2000-925203 | 20000411 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| NO 2001004927 | A | 20011213 | NO 2001-4927 | 20011010 |
| PRIORITY APPLN. INFO.: IT 1999-MI753 A 19990413 | | | | |
| WO 2000-EP3234 W 20000411 | | | | |

OTHER SOURCE(S): MARPAT 133:310142

AB Comps. A-B-C-N(O)s and A-Cl[N(O)s]-B1 or their salts [s is an integer 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacol. tests reported in the description; C and Cl are two bivalent radicals; the precursors of the radicals B and B1 are such as to meet the pharmacol. test reported in the description] were prepd. for use as pharmaceuticals. Thus, (S,S)-N-acetyl-S-(6-methoxy-.alpha.-methyl-2-naphthalenylacetyl)cysteine 4-nitroxybutyl ester was prepd. (NCX 2101) from naproxene and N-acetylcysteine in the first of 28 synthetic examples given. Pharmacol. test examples and tabular data are also given.

IT 9005-49-6, Dalteparin, reactions

RL: RCT (Reactant); RACT (Reactant or reagent)
 (drug precursor)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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 IT 50-33-9, Phenylbutazone, reactions 50-44-2, Mercaptopurine 50-59-9,

Cephaloridine 50-91-9, Floxuridine 51-21-8, Fluorouracil 51-43-4,
 Epinephrine 51-45-6, Histamine, reactions 53-79-2, Puromycin
 54-25-1, Azauridine 54-42-2, Idoxuridine 54-80-8, Pronethalol
 54-85-3, Isoniazid 56-75-7, Chloramphenicol 56-81-5D, Glycerol, iodo
 deriv. 57-08-9, .epsilon.-Acetamidocaproic acid 57-22-7, Vincristine
 57-27-2, Morphine, reactions 57-50-1, reactions 57-62-5 57-67-0,
Sulfaguanidine 57-68-1, Sulfamethazine 57-92-1, Streptomycin,
 reactions 58-32-2, Dipyridamole 59-05-2, Methotrexate 60-00-4,
 Edetic acid, reactions 60-54-8, Tetracycline 61-24-5, CephalosporinC
 61-33-6, Benzylpenicillinacid, reactions 61-68-7, Mefenamicacid
 61-72-3, Cloxacillin 63-74-1, Sulfanilamide 65-45-2 65-49-6,
 p-Aminosalicylic acid 66-79-5, Oxacillin 68-26-8, Vitamin A 68-35-9,
 Sulfadiazine 68-41-7, Cycloserine 68-88-2, Hydroxyzine 68-90-6,
 Benzydaron 69-33-0, Tubercidin 70-00-8, Trifluridine 72-14-0,
 Sulfathiazole 74-31-7, N,N'-Diphenyl-p-phenylenediamine 74-55-5,
 Ethambutol 74-79-3, Arginine, reactions 76-41-5, Oxymorphone
 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 77-07-6,
 Levorphanol 79-57-2, Oxytetracycline 80-02-4, 2-p-
 Sulfanilylanilinoethanol 80-03-5, Acediasulfone 80-08-0,
 4,4'-Sulfonyldianiline 80-32-0, Sulfachlorpyridazine 80-35-3,
 Sulfamethoxypyridazine 80-53-5, Terpin 84-16-2, Hexestrol 87-08-1,
 Penicillin V 87-09-2, Penicillin O 87-28-5, Glycolsalicylate
 89-45-2, Salicylsulfuricacid 90-05-1, Guaiacol 91-53-2, Ethoxyquin
 93-14-1, Guaifenesin 94-10-0, Ethoxazene 94-19-9, Sulfaethidole
 97-53-0, Eugenol 97-54-1, Isoeugenol 98-54-4 98-92-0, Nicotinamide
 100-55-0, Nicotiny alcohol 101-91-7, 4'-Hydroxybutyranilide 103-12-8,
 Sulfamidochrysoidine 103-97-9, Phenocoll 110-17-8, Fumaric acid,
 reactions 111-17-1, 3,3'-Thiodipropionic acid 113-98-4, Penicillin G
 potassiumsalt 114-07-8, Erythromycin 115-02-6, Azaserine 115-68-4,
 Sulfadicramide 116-42-7, Sulfaproxyline 116-44-9, Sulfapyrazine
 118-55-8, Phenyl salicylate 118-57-0, Acetaminosalol 119-98-2, Tocol
 120-53-0, n-Sulfanilyl-3,4-xylamide 121-00-6, 3-tert-Butyl-4-
 hydroxyanisole 121-79-9, Propyl gallate 122-11-2, Sulfadimethoxine
 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 127-07-1, Hydroxyurea
 127-33-3, Demeclocycline 127-35-5, Phenazocine 127-69-5, Sulfisoxazole
 127-71-9, Sulfabenzamide 127-79-7, Sulfamerazine 128-37-0,
 3,5-Di-tert-Butyl-4-hydroxytoluene, reactions 128-46-1,
 Dihydrostreptomycin 129-20-4, Oxyphenbutazone 130-16-5, Cloxyquin
 132-60-5, Cinchophen 132-92-3, Methicillinsodium salt 132-93-4,
 Phenethicillin potassium salt 133-11-9, Phenylaminosalicylate
 134-55-4, Phenylacetylsalicylate 136-70-9, Protokylol 138-52-3,
 Salicin 143-52-2, Metopon 144-14-9, Anileridine 144-80-9,
 Sulfacetamide 144-82-1, Sulfamethizole 144-83-2, Sulfapyridine
 147-94-4, Cytarabine 148-24-3, 8-Quinololinol, reactions 148-82-3,
 Melfalan 152-47-6, Sulfalene 153-61-7, Cephalothin 154-21-2,
 Lincomycin 154-42-7, Thioguanine 157-03-9, 6-Diazo-5-oxo-L-norleucine
 299-42-3, Ephedrine 302-79-4, Retinoic acid 303-81-1, Novobiocin
 305-03-3, Chlorambucil 315-30-0, Allopurinol 320-67-2, Azacitidine
 322-79-2, Triflusal 339-43-5, Carbutamide 359-83-1, Pentazocine
 389-08-2 390-64-7, Prenylamine 395-28-8, Isoxsuprine 404-86-4,
 Capsaicine 427-00-9, Desomorphine 437-74-1, Xanthinol niacinate
 443-48-1, Metronidazole 447-41-6, Nylidrin 456-59-7, Cyclandelate
 458-35-5 458-37-7, Curcumin 466-97-7, Normorphine 466-99-9,
 Hydromorphone 468-56-4, Hydroxypethidine 473-30-3, Thiazolsulfone
 477-30-5, Demecolcine 485-41-6, Sulfachrysoidine 486-79-3, Dipyroctyl
 487-48-9, Salacetamide 488-41-5, Mitobronitol 495-76-1, Piperonyl
 alcohol 495-84-1, Salinazid 497-75-6 498-71-5, Sobrerol 501-94-0,
 4-Hydroxyphenethyl alcohol 509-60-4, Dihydromorphine 515-49-1,
 Sulfathiourea 515-59-3, Sulfamethylthiazole 515-64-0, Sulfisomidine
 515-69-5, Bisabolol 518-28-5, Podophyllotoxin 519-37-9, Etofylline

525-94-0, Penicillin N 526-08-9, Sulfaphenazole 526-84-1,
 Dihydroxymaleic acid 530-08-5, Isoetharine 530-75-6,
 Acetylsalicylsalicylic acid 530-78-9, Flufenamic acid 533-73-3,
 Hydroxyhydroquinone 536-24-3, Ethylnorepinephrine 539-08-2,
 p-Lactophenetide 545-90-4, Dimepheptanol 547-44-4, Sulfanilylurea
 547-52-4, Sulfanilylsulfanilamide 547-53-5 551-27-9, Propicillin
 552-94-3, Salsalate 553-69-5, Benzenemethanol, ..alpha..-[(2-
 pyridinylamino)methyl]- 562-26-5, Phenoperidine 574-77-6, Papaveroline
 576-68-1, Mannomustine 577-85-5, 3-Hydroxyflavone 581-64-6, Thionine
 586-06-1, Metaproterenol 599-88-2, Sulfaperine 603-00-9, Proxiphylline
 610-88-8 632-00-8, Sulfasomizole 635-65-4, Bilirubin, reactions
 639-48-5, Nicomorphine 644-62-2, Meclofenamic acid 651-06-9, Sulfameter
 652-37-9, Acefylline 723-46-6, Sulfamethoxazole 729-99-7, Sulfamoxole
 751-97-3, Rolitetracycline 768-94-5, Amantadine 801-52-5, Porfiromycin
 808-26-4, Sancycline 824-46-4, Methoxyhydroquinone 840-50-6, MADU
 865-21-4, Vinblastine 959-10-4, Xenbucin 987-78-0, Citicoline
 992-21-2, Lymecline 1077-28-7, Thiocetic acid 1083-57-4, Bucetin
 1110-80-1, Pipacycline 1159-93-9, Clobenzepam 1174-11-4, Xenazoic acid
 1181-54-0, Clomocycline 1400-61-9, Nystatin 1403-28-7, Carzinophilin
 1403-66-3, Gentamicin 1404-04-2, Neomycin 1404-15-5, Nogalamycin
 1406-18-4, Vitamin E 1503-53-3, 5-Bromosalicylic acid acetate
 1531-12-0, Norlevorphanol 1553-60-2, Ibufenac 1596-63-0, Quinacillin
 1614-20-6, Nifurprazine 1695-77-8, Spectinomycin 1853-37-8,
 Podophyllic acid 1926-49-4, Clometocillin 1953-02-2, Tiopronin
 1984-94-7, Sulfasymazine 2013-58-3, Meclocycline 2016-63-9,
 Bamifylline 2030-63-9, Clofazimine 2055-44-9, Perisoxal 2179-16-0,
 Ninopterin 2315-08-4, Salazosulfadimidine 2316-64-5, Bromosaligenin
 2363-58-8, Epitiostanol 2373-80-0, 3,4-Methylenedioxycinnamic acid
 2447-57-6, Sulfadoxine 2750-76-7, Rifamide
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (drug precursor)

IT 2751-09-9, Troleandomycin 2779-55-7, Opiniazone 2809-21-4,
 Etidronic acid 2933-94-0, Toliprolol 3056-17-5, Stavudine 3094-09-5,
 Doxifluridine 3116-76-5, Dicloxacillin 3215-70-1, Hexoprenaline
 3485-14-1, Cyclacillin 3511-16-8, Hetacillin 3567-76-8 3572-43-8,
 Bromhexine 3577-01-3, Cephaloglycin 3590-05-4,
 Acetylsulfamethoxypyrazine 3611-72-1, Clobenfurol 3690-05-9,
 p-Coumaric alcohol 3691-74-5, Glyconiazide 3703-79-5, Bamethan
 3733-81-1, Defosfamide 3734-52-9, Metazocine 3772-76-7,
 Sulfamethomidine 3811-25-4 3820-67-5, Glafenine 3922-90-5,
 Oleandomycin 3930-19-6, Streptonigrin 3930-20-9, Sotalol 4008-48-4,
 Nitroxoline 4097-22-7, Dideoxyadenosine 4393-19-5 4394-00-7,
 Niflumic acid 4564-87-8, Carbomycin 4697-36-3, Carbenicillin
 4803-27-4, Anthramycin 5205-82-3, Bevoniummethylsulfate 5250-39-5,
 Floxacillin 5486-77-1, Alloclamide 5536-17-4, Vidarabine 5581-52-2,
 Thiamiprine 5633-20-5, Oxybutynin 5638-76-6, Betahistine 5728-52-9,
 Felbinac 5741-22-0, Moprolol 5934-14-5, Succisulfone 6064-83-1,
 Fosfosal 6135-36-0, 1-Butyl-3-methylurea 6202-21-7,
 4-Sulfanilamidosalicylic acid 6452-71-7, Oxprenolol 6489-97-0,
 Metampicillin 6621-47-2, Perhexiline 6673-35-4, Practolol 6946-29-8,
 P-Aminosalicylic acidhydrazide 6998-60-3, Rifamycin 7413-36-7,
 Nifenalol 7481-89-2, Zalcitabine 7542-37-2, Paromomycin 8025-81-8,
 Spiramycin 9005-49-6, Dalteparin, reactions 9041-08-1,
 Reviparin sodium 10118-90-8, Minocycline 10318-26-0, Mitolactol
 11003-38-6, Capreomycin 11006-76-1, Virginiamycin 11120-15-3,
 Dermostatin 12650-69-0, Mupirocin 13042-18-7, Fendiline 13292-46-1,
 Rifampin 13392-18-2, Fenoterol 13392-28-4, Rimantadine 13411-16-0,
 Nifurpirinol 13523-86-9 13642-52-9, Soterolol 13655-52-2, Alprenolol
 13665-88-8, Mopidamol 13710-19-5, Tolfenamic acid 13739-02-1, Diacerein
 13741-18-9, Xibornol 13799-03-6, Protizinic acid 13838-08-9,

Azidamfenicol 13898-58-3, Benzoylpas 13925-12-7, Myxin 13946-02-6,
 Metron S 13993-65-2, Metiazinicacid 14556-46-8, Bupranolol
 14838-15-4, Phenylpropanolamine 15176-29-1, Edoxudine 15307-79-6,
 Sodium diclofenac 15468-10-7, Oxidronic acid 15599-51-6, Apicycline
 15686-71-2, Cephalixin 15722-48-2, Olsalazine 16110-51-3 16545-11-2,
 Guamecycline 16846-24-5, Josamycin 17243-38-8, Azidocillin
 17737-65-4, Clonixin 17784-12-2, Sulfacytine 17969-20-9, Fenclozicacid
 18046-21-4, Fentiazac 18323-44-9, Clindamycin 18378-89-7, Plicamycin
 18471-20-0, Ditazol 18699-02-0, Actarit 18883-66-4, Streptozocin
 19562-30-2, Piromidicacid 19767-45-4, Mesna 20168-99-4, Cinmetacin
 20187-55-7, Bendazac 20594-83-6, Nalbuphine 20830-81-3, Daunorubicin
 21256-18-8, Oxaprozin 21679-14-1, Fludarabine 22006-84-4, Denopterine
 22071-15-4, Ketoprofen 22103-14-6, Bufeniode 22131-79-9, Alclofenac
 22254-24-6, Ipratropiumbromide 22494-42-4, Diflunisal 22664-55-7,
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 Salicylamide O acetic acid 25546-65-0, Ribostamycin 25803-14-9,
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 26171-23-3, Tolmetin 26774-90-3, Epicillin 26787-78-0, Amoxicillin
 26839-75-8, Timolol 26973-24-0, Ceftezole 27031-08-9, Sulfaguanole
 27203-92-5, Tramadol 27470-51-5, Suxibuzone 27726-31-4, Pivcephalexin
 27762-78-3, Kethoxal 28657-80-9, Cinoxacin 29122-68-7, Atenolol
 29679-58-1, Fenoprofen 29767-20-2, Teniposide 30187-90-7, Xibenolol
 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 30418-38-3,
 Tretoquinol 30516-87-1, Zidovudine 30544-47-9, Etofenamate
 30653-83-9, Parsalimide 31127-82-9, Iodoxamide 31698-14-3, Ancitabine
 31793-07-4, Pirprofen 31842-01-0, Indoprofen 32385-11-8, Sisomicin
 32527-55-2, Tiaramide 32665-36-4, Eprozinol 32808-51-8, Bucloxic acid
 32887-01-7, Amdinocillin 32909-92-5, Sulfametrole 32953-89-2,
 Rimiterol 32986-56-4, Tobramycin 32988-50-4, Viomycin 33005-95-7,
 Tiaprofenicacid 33069-62-4, Paclitaxel 33103-22-9, Enviomycin
 33159-27-2, Ecabet 33369-31-2, Zomepirac 33404-78-3, Negamycin
 33419-42-0, Etoposide 33817-20-8, Pivampicillin 33996-33-7, Oxaceprol
 34148-01-1, Clidanac 34444-01-4, Cefamandole 34493-98-6, Dibekacin
 34552-84-6, Isoxicam 34661-75-1, Urapidil 34675-84-8, Cetraxate
 34787-01-4, Ticarcillin 34866-47-2, Carbuterol 34915-68-9, Bunitrolol
 34919-98-7, Cetamolol 35457-80-8, Midecamycin 35531-88-5,
 Carindacillin 35607-66-0, Cefoxitin 36330-85-5, Fenbufen 36702-83-7,
 Tinofedrine 36791-04-5, Ribavirin 36894-69-6, Labetalol 36981-91-6,
 Fepradinol 37091-66-0, Azlocillin 37148-27-9, Clenbuterol
 37321-09-8, Apramycin 37517-28-5, Amikacin 37517-30-9, Acebutolol
 37762-06-4, Zaprinast 38129-37-2, Bicozamycin 38194-50-2, Sulindac
 38363-40-5, Penbutolol 38677-81-5, Pirbuterol 38677-85-9, Flunixin
 38821-53-3, Cephradine 39324-30-6, Pepstatin 39718-89-3, Alminoprofen
 39809-25-1, Penciclovir 40391-99-9, Pamidronicacid 40828-46-4,
 Suprofen 41340-25-4, Etodolac 41570-61-0, Tulobuterol 41744-40-5,
 Sulbenicillin 42200-33-9, Nadolol 42408-82-2, Butorphanol
 42779-82-8, Clopirac 42794-76-3, Midodrine 42835-25-6, Flumequine
 47747-56-8, Talampicillin 50264-69-2, Lonidamine 50270-33-2,
 Isofezolac 50370-12-2, Cefadroxil 50679-08-8, Terfenadine
 50935-04-1, Carubicin 50972-17-3, Bacampicillin 51025-85-5, Arbekacin
 51384-51-1, Metoprolol 51395-42-7, Butedronic acid 51481-61-9,
 Cimetidine 51481-65-3, Mezlocillin 51579-82-9, Amfenac 51627-14-6,
 Cefatrizine 51762-05-1, Cefroxadine 51781-06-7, Carteolol
 51940-44-4, Pipemidicacid 52081-33-1, Mitomycins 52093-21-7,
 Micronomicin

RL: RCT (Reactant); RACT (Reactant or reagent)

KRISHNAN 09/909,797

(drug precursor)

=> d ibib abs hitstr 4

L56 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1997:477885 HCAPLUS
 DOCUMENT NUMBER: 127:162048
 TITLE: Modifications under basic conditions of the minor
 sequences of heparin containing 2,3- or 2,3,6-sulfated
 D-glucosamine residues
 AUTHOR(S): Santini, Francesco; Bisio, Antonella; Guerrini, Marco;
 Yates, Edwin A.
 CORPORATE SOURCE: Istituto di Chimica e Biochimica "G. Ronzoni", Milan,
 20133, Italy
 SOURCE: Carbohydrate Research (1997), 302(1-2), 103-108 ←
 CODEN: CRBRAT; ISSN: 0008-6215
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The ¹H NMR chem. shift assignments are reported for 2,3-di- or
 2,3,6-tri-sulfated glucosamine in a sample of high affinity (for
 antithrombin III) heparin in three distinct environments. Following
 treatment in **strong basic** conditions the disappearance
 of these signals and the appearance of new signals consistent with the
 formation of N-sulfo-2,3-aziridine contg. amino sugar residues is
 demonstrated. Anti-factor Xa activity of sulfoaziridine heparin were
 performed using a chromogenic endpoint assay employing an accucolor
 heparin kit.
 IT **9005-49-6**, Heparin, reactions
 RL: **RCT (Reactant)**; RACT (Reactant or reagent)
 (intramol. cyclocondensation aziridination of the minor sequences of
 heparin contg. 2,3- or 2,3,6-sulfated D-glucosamine residues)
 RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)
 *** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 5

L56 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1989:417717 HCAPLUS

DOCUMENT NUMBER: 111:17717

TITLE: Low-molecular-weight heparins with a regular structure, their preparation and biological uses

INVENTOR(S): Lormeau, Jean Claude; Petitou, Maurice; Choay, Jean; SANOFI

PATENT ASSIGNEE(S): SANOFI, Fr.

SOURCE: Eur. Pat. Appl., 19 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

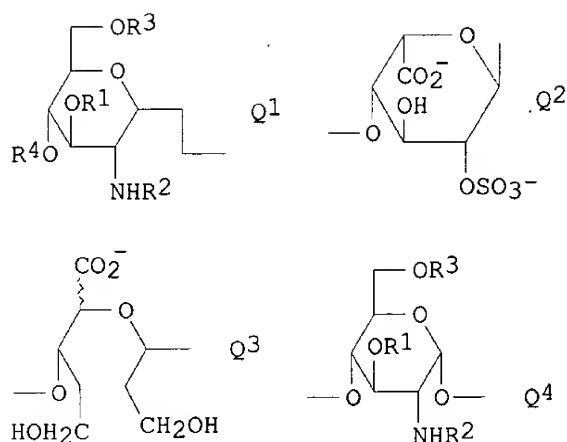
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 287477 | A2 | 19881019 | EP 1988-400928 | 19880415 |
| EP 287477 | A3 | 19890726 | | |
| EP 287477 | B1 | 19941102 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| FR 2614026 | A1 | 19881021 | FR 1987-5457 | 19870416 |
| FR 2614026 | B1 | 19920417 | | |
| FI 8801783 | A | 19881017 | FI 1988-1783 | 19880415 |
| FI 88046 | B | 19921215 | | |
| FI 88046 | C | 19930325 | | |
| NO 8801660 | A | 19881017 | NO 1988-1660 | 19880415 |
| NO 170940 | B | 19920921 | | |
| NO 170940 | C | 19921230 | | |
| AU 8814663 | A1 | 19881020 | AU 1988-14663 | 19880415 |
| AU 601566 | B2 | 19900913 | | |
| JP 63278901 | A2 | 19881116 | JP 1988-91891 | 19880415 |
| ZA 8802662 | A | 19881130 | ZA 1988-2662 | 19880415 |
| US 4990502 | A | 19910205 | US 1988-181969 | 19880415 |
| CA 1327968 | A1 | 19940322 | CA 1988-564296 | 19880415 |
| DK 8802103 | A | 19881017 | DK 1988-2103 | 19880418 |
| DK 173982 | B1 | 20020325 | | |

PRIORITY APPLN. INFO.:

FR 1987-5457 A 19870416

GI



AB A low-mol.-wt. heparin, R(XY)nR' [I; R = H, Q1; X = Q2, Q3; Y = Q4; R1 = H, SO3⁻; R2 = Ac, SO3⁻ (.apprx.90%); R3 = H, SO3⁻ (.apprx.70%); R4 = H, uronic acid; R' = H, natural uronic acid, oxidized uronic acid with aldehyde groups reduced to alcs.; n = 7-15], of .apprx.4800-9000 mol. wt., is prepd. by (1) treating an aq. soln. of heparin (0.5-5%, wt./vol.) with HIO4 (0.5-4%, wt./vol.) at pH 4.5-6.5 and 0-10.degree.; (2) treating the heparin chains obtained with 0.1-0.3N **strong base**; (3) treating the **depolymd.** fragments with a reducing agent; (4) eliminating the excess reducing agent and pptg. the fragments with a mineral salt and an alc.; (5) recovering the product and converting it to a pharmaceutically acceptable salt. I does not have anticoagulant activity and is useful as a medicament for regulating certain physiol. systems. Porcine heparin Na salt (10 g) was treated with NaIO4 at pH 5.0 and 4.degree. for 24 h in the dark, the residual IO4⁻ was removed by dialysis, and the modified heparin was **depolymd.** with 10N soda for 3 h at 18-21.degree.. The product was reduced with NaBH4 and then fractionated by repeated pptn. with NaCl-contg. EtOH, to give 5.0 g product (IC 1772). IC 1772 inhibited the proliferation of rat smooth muscle cells in vitro and in vivo similarly to heparin std., inhibited the formation of complement C 3b-protein B complex with a 50% inhibitory concn. of 0.4 .mu.g/mL (heparin value = 0.5 .mu.g/mL), and administered i.v. to rabbits at 1 mg/kg had antithrombotic activity in all 10 animals.

IT **9005-49-6P**, Heparin, biological studies
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (low-mol.-wt., modified, prepn. of)
 RN 9005-49-6 HCAPLUS
 CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ind 5

L56 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2002 ACS

IC ICM C08B037-10

ICS A61K031-725

CC 1-8 (Pharmacology)

Section cross-reference(s): 9, 15

ST heparin deriv antithrombotic complement inhibitor; smooth muscle inhibitor
 heparin deriv

IT Cell division
(by smooth muscle, low-mol.-wt. modified heparin inhibition of)
IT Anticoagulants and Antithrombotics
(low-mol.-wt. modified heparin)
IT Muscle
(smooth, proliferation of, low-mol.-wt. modified heparin inhibition of)
IT 80295-43-8D, Complement C 3b, factor B complexes 80295-62-1D, Complement
factor B, complement C 3b complexes
RL: FORM (Formation, nonpreparative)
(formation of, low-mol.-wt. modified heparin inhibition of)
IT 9005-48-5P, Potassium heparin **9005-49-6P**, Heparin, biological
studies 9041-08-1P, Sodium heparin 37270-89-6P, Calcium heparin
54479-70-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(low-mol.-wt., modified, prepn. of)

=> d ibib abs hitstr 6

L56 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1987:595609 HCAPLUS

DOCUMENT NUMBER: 107:195609

TITLE: Neutralization and binding of heparin by S protein/vitronectin in the inhibition of factor Xa by antithrombin III. Involvement of an inducible heparin-binding domain of S protein/vitronectin

AUTHOR(S): Preissner, Klaus T.; Mueller-Berghaus, Gert

CORPORATE SOURCE: Clin. Res. Unit Blood Coagulation Thromb., Justus-Liebig-Univ., Giessen, D-6300, Fed. Rep. Ger.

SOURCE: J. Biol. Chem. (1987), 262(25), 12247-53 ← X
CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The interference of the heparin-neutralizing plasma component S protein (vitronectin) (mol. wt. (Mr) = 78,000) with heparin-catalyzed inhibition of coagulation factor Xa by antithrombin III (ATIII) was investigated in human plasma and in a purified system. In plasma, S protein effectively counteracted the anticoagulant activity of heparin, since factor Xa inhibition was markedly reduced in comparison to heparinized plasma deficient in S protein. By using purified components in the presence of heparin, S protein induced a concn.-dependent redn. of the inhibition rate of factor Xa by ATIII. This resulted in a decrease of the apparent pseudo-1st order rate const. by >10-fold at a physiol. ratio of ATIII to S protein. S protein not only counteracted the anticoagulant activity of com. heparin but also of low-Mr forms of heparin (mean Mr of 4500). The heparin-neutralizing activity of S protein was mainly expressed in the range 0.2-10 .mu.g/mL of high-Mr as well as low-Mr heparin. S protein and high-affinity heparin reacted with apparent 1:1 stoichiometry to form a complex with a dissozn. const. $KD = 1 \times 10^{-8}M$ as detd. by a functional assay. As deduced from dot-blot anal., direct interaction of radiolabeled heparin with S protein revealed a $KD = 4 \times 10^{-8}M$. Heparin binding as well as heparin neutralization by S protein increased significantly when reduced/carboxymethylated or guanidine-treated S protein was employed, indicating the existence of a partly buried heparin-binding domain in native S protein. Radiolabeled heparin bound to the native protein mol. as well as to a BrCN fragment (Mr = 12,000) contg. the heparin-binding domain as demonstrated by direct binding on nitrocellulose replicas of SDS-polyacrylamide gels. Kinetic anal. revealed that the heparin neutralization activity of S protein in the inhibition of factor Xa by ATIII could be mimicked by a synthetic tridecapeptide from the N-terminal portion of the heparin-binding domain. Hence, the heparin-binding domain of S protein appears to be unique in binding to heparin and thereby neutralizing its anticoagulant activity in the inhibition of coagulation factors by ATIII. The induction of heparin binding and neutralization may be considered a possible physiol. mechanism initiated by conformational alteration of the S protein mol. Consequently, a secondary structure model of S protein is proposed in which the .beta.-pleated sheet structure of the heparin-binding domain is localized in a buried position within the protein mol.

IT 9005-49-6, Heparin, biological studies

RL: RCT (Reactant)

(vitronectin binding and neutralization of, in blood-coagulation factor Xa inhibition by antithrombin III)

RN 9005-49-6 HCAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

KRISHNAN 09/909,797

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d ibib abs hitstr 1

L107 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:219836 HCAPLUS

DOCUMENT NUMBER: 128:286337

TITLE: Processes for the preparation of low-affinity, low molecular weight heparins useful as antithrombotics

INVENTOR(S): Hirsh, Jack; Shaklee, Patrick N.; Knobloch, James E.; Weitz, Jeffrey I.; Young, Edward

PATENT ASSIGNEE(S): Hamilton Civic Hospitals Research Development Inc., Can.; Shaklee, Patrick N.; Knobloch, James E.; Weitz, Jeffrey I.; Young, Edward

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 9814481 | A1 | 19980409 | WO 1997-US17849 | 19971001 |
| <p>W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM</p> <p>RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG</p> | | | | |
| US 5767269 | A | 19980616 | US 1996-722408 | 19961001 |
| AU 9747441 | A1 | 19980424 | AU 1997-47441 | 19971001 |
| PRIORITY APPLN. INFO.: | | | US 1996-722408 | 19961001 |
| | | | WO 1997-US17849 | 19971001 |

AB The present invention generally relates to processes for prep. low affinity, low mol. wt. heparins (LA-LMW-heparins) which are endowed with pharmacol. and therapeutic properties that are surprisingly advantageous. In one embodiment, the process comprises: (1) nitrous acid depolymn. of unfractionated **heparin** to yield low mol. wt. **heparin** (**LMWH**); (2) oxidn. of the resulting **LMWH** to open the ring structures the **nonsulfated uronic acid** moieties using, for example, **sodium** periodate; and (3) redn. of the oxidized **LMWH** to reduce the aldehydes (to alcs.) formed during the depolymn. and oxidn. steps using, for example, **sodium** borohydride. The resulting LA-LMW-heparins are capable of inactivating thrombin bound to fibrin within a thrombus or clot, whereby the ability of clot-bound thrombin to catalytically promote further clot accretion is substantially diminished or eliminated. As such, the resulting LA-LMW-heparins are useful for preventing thrombosis in the circuit of cardiac bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from thrombus-related cardiovascular conditions, such as unstable angina, acute myocardial infarction (heart attack), cerebrovascular accidents (stroke), pulmonary embolism, deep vein thrombosis, arterial thrombosis, etc.

=> d ibib abs hitstr 2

L107 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:614342 HCAPLUS

DOCUMENT NUMBER: 125:265104

TITLE: Interaction between the **sulfated** lactobionic acid (LW 10082) and other antithrombotic agents in animal thrombosis model

AUTHOR(S): Giedrojć, Jan; Krupinski, Kazimierz; Breddin, Hans Klaus; Bielawiec, Michal

CORPORATE SOURCE: Department Haematology, Medical Academy, Bialystok, 15-276, Pol.

SOURCE: Pol. J. Pharmacol. (1996), 48(3), 317-322 ←

CODEN: PJPAE3; ISSN: 1230-6002

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We investigated the comparative antithrombotic properties of LW 10082, acetylsalicylic acid (Aspisol), low mol. wt. **heparin** (**LMWH**, CY 216) and **sodium heparin** using laser-induced thrombosis model. The animal model which has been used is well suited to observe platelet reactions to damaged endothelial cells and also to evaluate the effect of drugs on the formation of platelet thrombi. The rat mesenteric venules with a diam. of 20-30 .mu.m were injured by well defined argon laser lesion. The no. of laser injuries which were needed to induce a thrombus intermittently occluded the vessel was counted to quantitate the results. LW 10082 was injected s.c. 2 h prior to testing. The minimal ED of LW 10082 which significantly inhibited thrombus formation was 5 mg/kg. The antithrombotic effect of Aspisol has been investigated after its oral application at doses of 1, 5 and 10 mg/kg 2 h before studying the antithrombotic effect. The minimal ED for Aspisol was 10 mg/kg. The **LMWH** has been injected into the rat tail vein in doses of 1, 0.2 and 0.1 mg/kg 30 min before testing, 0.1 mg/kg did not have any antithrombotic effect. The minimal ED of the **sodium heparin** which significantly inhibited thrombus formation was 20 U/kg measured 30 min after its i.v. injection. The combination of minimal ED of LW 10082 and **LMWH** had a significant additive effect. There was a slight but not significant additive effect between LW 10082, Aspisol and **heparin sodium**. Our results suggest that combinations of LW10082 with **LMWH** may provide a new approach to more effective prophylaxis and treatment of venous or arterial thrombosis.

=> d ibib abs hitstr 3

L107 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1995:455068 HCAPLUS

DOCUMENT NUMBER: 122:209022

TITLE: Fluorescence and circular dichroism studies during the interactions of **sulfated** polysaccharides with antithrombin III

AUTHOR(S): Tanyi, A.; Benjamin, V.; Sadberry, A. J.; Doctor, V. M.

CORPORATE SOURCE: Dep. Chemistry, Prairie View A and M University, Prairie View, TX, 77446, USA

SOURCE: Thromb. Res. (1995), 77(6), 505-13
CODEN: THBRAA; ISSN: 0049-3848

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The changes in relative fluorescence of antithrombin III (AT-III) during its interaction with **sulfated** xylans were compared with that of **sulfated** glycosaminoglycans by measuring the ratio of the increase in fluorescence of AT-III in the presence of **sulfated** polysaccharide to the fluorescence of AT-III alone for various mass ratios. Interactions of corn cob xylan **sulfate** (CCXS) and **sodium** pentosan **polysulfate** (SP-54) with AT-III resulted in enhancements of relative fluorescence which were lower than com. **heparin**. At mass ratios below 1, **heparan sulfate** and low mol. wt. **heparin** (**LMWH**) gave increases in the relative fluorescence higher than that of com. **heparin**, while highly **sulfated** semisynthetic chondroitin **sulfates** A and C gave much smaller increases. The relative fluorescence enhancements of AT-III by **heparan sulfate**, com. **heparin**, **LMWH** and **heparin** derived pentasaccharide (HDP) increased with increasing mass ratios while the enhancements by CCXS, SP-54 and the highly **sulfated** chondroitin **sulfates** A and C were reversed at higher mass ratios. The estd. dissocn. consts. (kd) for the interaction of AT-III and the **heparin**-related compds. showed that **heparan sulfate** and **LMWH** gave the lowest kd values indicating a higher affinity for AT-III while com. **heparin** and HDP gave higher kd values, indicating a lower affinity for AT-III. SP-54 gave a kd value lower than CCXS, indicating a greater affinity for AT-III. A comparison of the near UV CD spectrum of AT-III alone and during its interaction with oat spelts xylan **sulfate** showed enhancements of the 2 arom. amino acid regions corresponding to phenylalanine and tryptophan.